THE PREPARATION OF SOME SUBSTITUTED 1,2,4-TRIAZOLINE-5-THIONES FROM HYDRAZINE DERIVATIVES.

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ABSTRACT

THE PREPARATION OF SOME SUBSTITUTED 1,2,4-TRIAZOLINE-5-THIONES FROM HYDRAZINE DERIVATIVES

A. Wayne Cascarano

The reaction of phenyl and methyl isothiocyanate with a series of monosubstituted hydrazines in absolute ethanol has been studied. The reaction temperatures as well as the substituent on the hydrazine molecule was found to effect the distribution of isomeric thiosemicarbazide products obtained.

The isomerization of several 2,4-disubstituted thiosemicarbazides to their 1,4 isomers was investigated, and evidence has been presented which suggests that an intramolecular isomerization pathway is involved.

Substituted 1,2,4-triazoline-5-thiones were produced from thiosemicarbazides by benzoylating the thiosemicarbazide and cyclizing the product in base, or by directly reacting the thiosemicarbazide with ethyl formate in an alkaline media. The substituted triazoline-5-thiones were then S-alkylated with ethyl monochloroacetate to yield the corresponding 1,2,4-triazolyl-5-mercapto acetates. The acetate group was further built up into a benzoyl thiosemicarbazide structure. The resulting compound was cyclized in basic media to form a novel 1,2,4-triazole-1,2,4-triazoline-5-thione type compound linked by a methyl mercapto group. Acid cyclization of the substituted thiosemicarbazide resulting in a 1,2,4-triazole-1,3,4-thiadiazole type compound linked by a methyl mercapto group.

The structures of the intermediates and products were verified and studied by spectroscopic methods.

TO MY MOTHER AND FATHER

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to his Research Director, the late Prof. Jacques Lenoir, to the members serving on his committee, Dr. Zacharias Hamlet and Dr. N. Serpone, and to the Chemistry Department for the facilities afforded throughout the course of this work.

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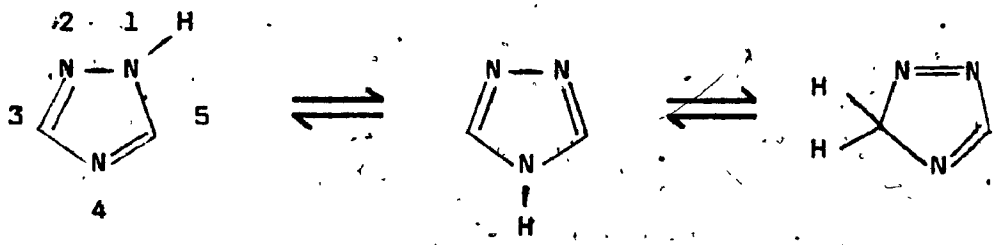
GENERAL INTRODUCTION

THE 1,2,4-TRIAZOLE RING SYSTEM

Nomenclature

Five-membered ring systems containing three nitrogen atoms and two carbon atoms are known as triazoles. These may be of two types, the 1,2,3-triazole or V-triazole (Vicinal) and the 1,2,4-triazole or S-triazole (Symmetric).[1-5] Derivatives of the latter type are the subject of this thesis.



I II III

1,2,4-triazole

For those derivatives with N-substituents, the relationship to the parent form is signified by describing them as 1,2,4-1H-triazoles (structure I) or as 1,2,4-4H-triazoles (structure II). This is based on the assumption that 1,2,4-triazole is capable of existing as two tautomeric forms, I and II.

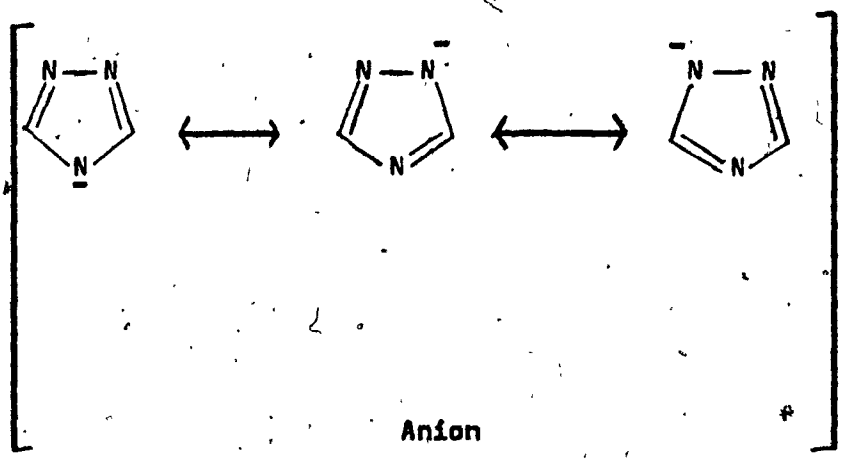
Historically the name triazole was given to this ring system by Bladin, who described derivatives of it in 1885.[6]

Physical Properties and Structure.

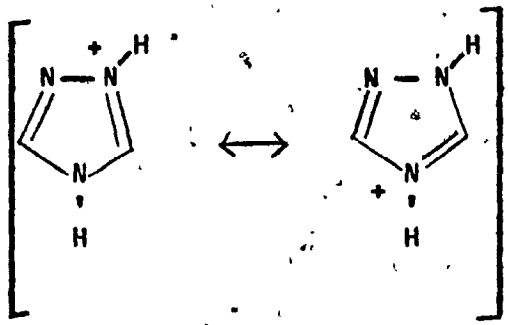
Referring to table I, a comparison of boiling points, and dipole moments of 1,2,4-triazole with other 5-membered hetrocycles, gives evidence of its considerable polar nature.[1] The boiling point of 1,2,4-triazole is considerably higher in comparison with those of furan and pyrrole, though their molecular weights are similar. It can also be seen in table 1, that the introduction of a methyl group onto the 1-position of 1,2,4-triazole lowers the boiling point by 82°C and the melting point by 101°C, whereas the introduction of a 3-methyl substituent makes no appreciable difference. This indicates the presence of an associated N-H group. On analysis of the infrared spectra of 1,2,4-triazole and its derivatives containing an unsubstituted N-H group, it has been suggested that the solid state structure of these triazoles consist of a pair of ions which are intermolecularly associated.[7,8] The hydrogen atom of the imino group protonates an unsaturated nitrogen of an adjacent molecule, the various canonical forms of the two charged particles, are shown on page 4.

TABLE I. PHYSICAL CONSTANTS OF SEVERAL FIVE-MEMBERED HETEROCYCLES.[1]

COMPOUND	MELTING POINT	BOILING POINT AT 760mm	DIPOLE MOMENT
	°C	°C	D
Furan	--	32	0.63
Pyrrole	--	131	1.80
Thiophene	--	84	0.54
1,2,4-Triazole	121	260	3.17
1-Methyl-1,2,4-1H-Triazole	20	178	--
3-Methyl-1,2,4-Triazole	95	265	--



Anion

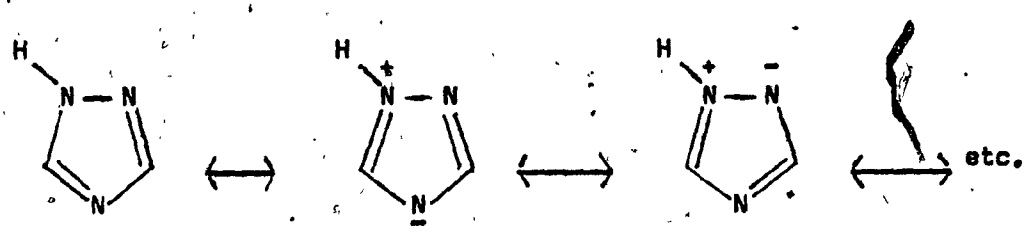


Cation

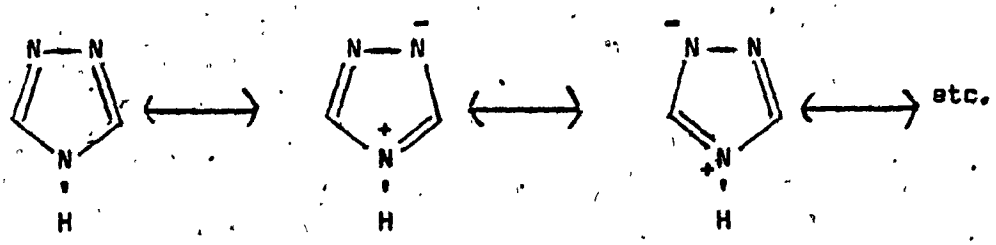
This suggestion was made because of the presence of two bands in the infrared spectrum of 1,2,4-triazole, a broad ammonium-type band at 2860-2500cm^{-1} and an immonium-type band at 1818cm^{-1}, characteristic of the following structural moiety. [9]

1,2,4-Triazole has an extremely stable nucleus which is regarded as aromatic in nature, and whose two tautomeric forms are resonance stabilized.

Tautomer I.



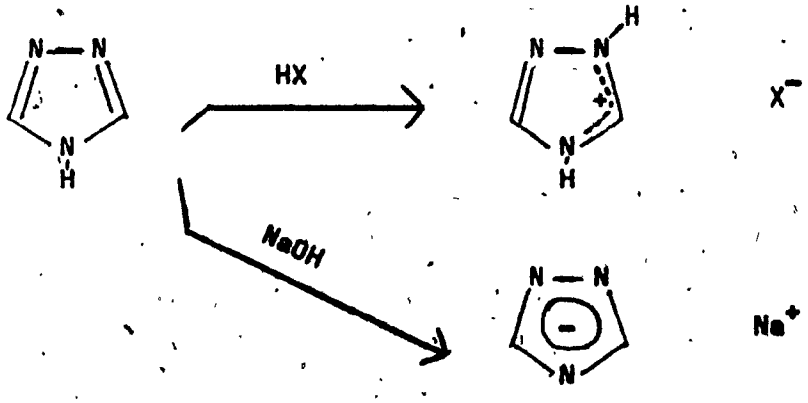
Tautomer II.



In the solid phase, tautomer I is favoured as the more stable over the symmetrical tautomer II, by x-ray crystallographic determinations.[10,11] Similarly from microwave spectroscopy in the vapour phase tautomer I was found to predominate.[12] Ionization constants of I and 4-alkyl derivatives of 1,2,4-triazoles have indicated the ratio of tautomer I to II to be about 5-10:1.[13]

Room temperature NMR spectra of 1,2,4-triazole in $CDCl_3$ or D.M.S.O. yield singlets, the NH protons are not observed with normally purified solvents. Thus it has been concluded that the time averaged picture of the molecule must be symmetrical.[14] In very dry solvents, however, the signal from the N-H proton is sharp enough to be observed and in carefully distilled H.M.P.T.*, two distinct C-H peaks are observed at temperatures below 0°. In a 4.3% solution, a maximum separation of 56 H_z (at 60 MH_z) is observed at -34°. Such a separation of peaks has been interpreted in terms of the predominance of the 1-H tautomer (tautomer I) over the 4-H tautomer.[15]

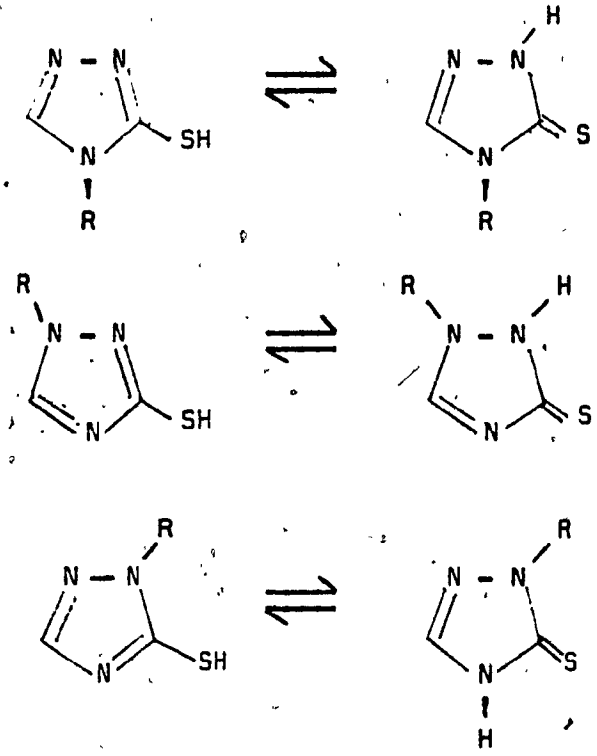
1,2,4-triazoles are amphoteric in nature, forming salts with both acids and bases.



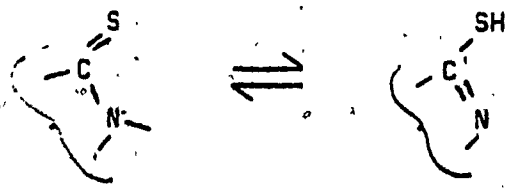
* Hexamethylphosphoric triamide

SUBSTITUTED MERCAPTO TRIAZOLES.

5-Mercapto 1,2,4-triazoles are potentially tautomeric. The following 3 isomers, each capable of existing in two tautomeric forms, are possible for compounds with a nitrogen substituent.

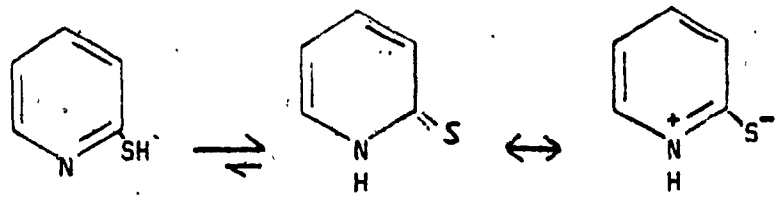


In general, ∝ mercapto derivatives of N-heteroaromatic compounds are capable of this thione-thiol protomeric equilibria.



Thione Thiol

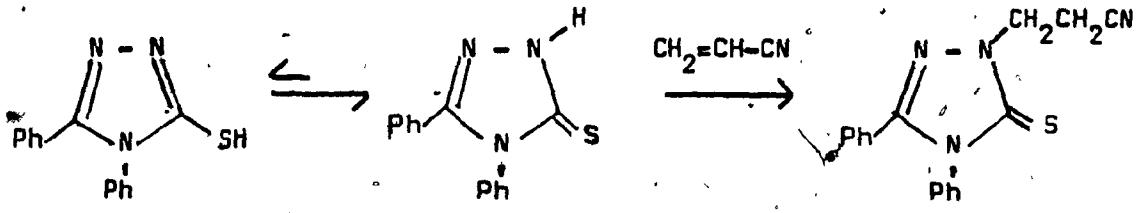
2 — Mercapto pyridine, for example, has been found to be present in water principally in the thione form by a comparison of its UV spectra with those of its N-methyl and S-methyl derivatives.[16]

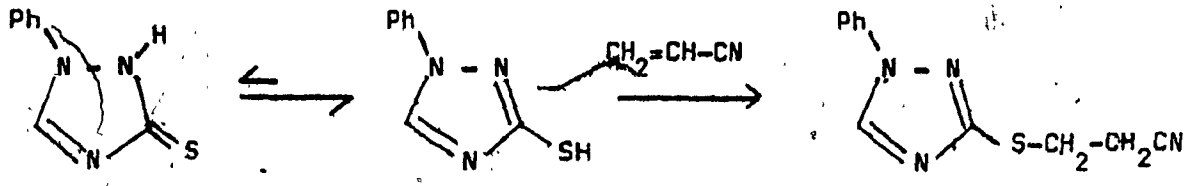


Later, infrared studies of 2-mercapto pyridine and similar α mercapto derivitives of N-Heteroaromatic compounds show that they exist in the thione form, both in the solid state and in solvents of low polarity.[17]

Similarly, the presence of bands at 1330cm^{-1} for C=S and at 1548cm^{-1} for the NHC=S group in the IR spectra of 4-aryl-3 aryl amino 1,2,4-triazoline-5-thiones, indicate the predominance of the thione structure.[18] Recently, however, E.G. Kavalev, et al, have demonstrated that the position of N-phenyl substituents on the triazole ring plays an essential role in this tautomerism.[19] The cyanoethylation of 1-phenyl 1,2,4-triazoline-5-thione, as well as the 3,4-diphenyl derivative, in alcohol in the presence of triethylamine, lead to the formation of N-cyanoethyl derivatives. However, the cyanoethylation of 2-phenyl-1,2,4-triazoline-5-thione lead to the formation of S-cyanoethyl derivative.

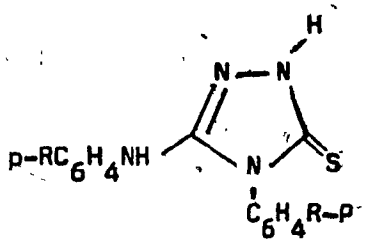
Cyanoethylation generally occurs by a 1,4-nucleophilic addition to acrylonitrile.[20]

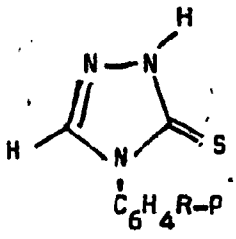




Acidity constants have been reported for some mono- and disubstituted 1,2,4-triazoline-5-thiones, and they are presented in table II. These constants were determined by potentiometric titration of aqueous alcohol solutions.[18] It can be seen that replacement of hydrogen in the 3-position of the 1,2,4-triazoline-5-thione ring by an arylamino group leads to a decrease in the acidity by two orders of magnitude as compared with 4-aryl-1,2,4-triazoline-5-thione. It can also be seen that the chlorine atom in the 4-position of the phenyl ring displays an

TABLE II Acidity constants of 1,2,4-triazoline-5-thione derivatives.





R	pK_a	pK_a
H	8.39	6.80
CL	8.47	6.60
C_2H_5O	9.15	7.20

electron-accepting effect and increases the acidity of the compound, while the electron-donating ethoxy group lowers the acidity of the triazole derivatives.

USES

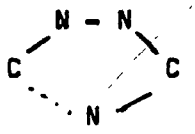
Various 1-acyl-4-substituted thiosemicarbazides are known to posses biological properties like antitubercular,[21] antifungal[22] and hypoglycemic[23] activities. Heterocycles derived from these compounds, such as oxadiazoles, thiadiazoles and 1,2,4-triazoline-5-thiones are important chemotherapeutic agents and have been reported to exhibit antitubercular,[24] diuretic,[25] bacteriostatic,[26] hypoglycemic,[27] antiviral,[28] antifungal,[29] antithyroid[30] and herbicidal[31] action. Finally 1,2,4-triazoline-5-thiones are important synthetic intermediates since they can be readily converted to the parent structure with such reagents as hydrogen peroxide[32].

SYNTHETIC ROUTES

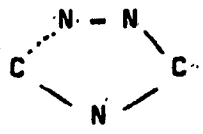
Substituted 5-mercapto 1,2,4-triazoles have been prepared by various intermolecular and intramolecular condensation pathways, as briefly outlined below:

I Intramolecular Condensation

Two main routes, type A and type B, have been used to produce substituted 5-mercapto triazoles:

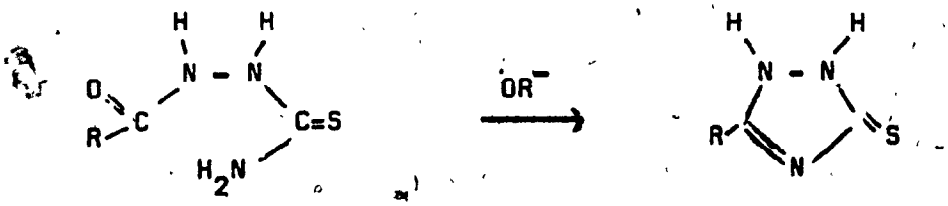


Type A



Type B

Type A ring closure has become established as the most efficient method of synthesis of C-monosubstituted thiatriazoles. An example is the cyclization of 1-acyl-thiosemicarbazides in alkaline solution.[33]

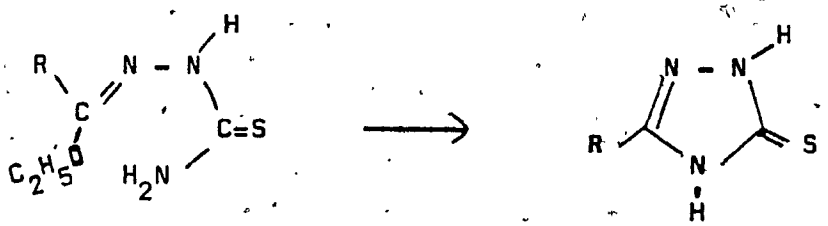


By the acylation of thiosemicarbazide with the appropriately substituted acid chloride, a variety of intermediates for this type

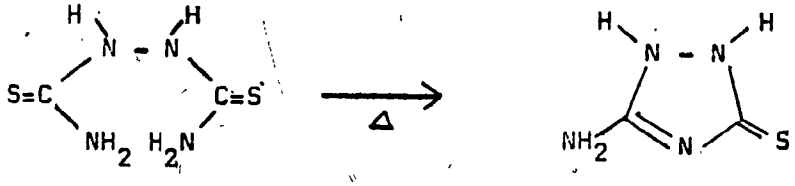
of ring closure may be obtained.[34-38]

Similarly, 3,4-disubstituted 1,2,4-triazoline-5-thiones are efficiently prepared from the cyclization of 1-acyl-4-substituted-thiosemicarbazides with alkali or by heat.[39-40]

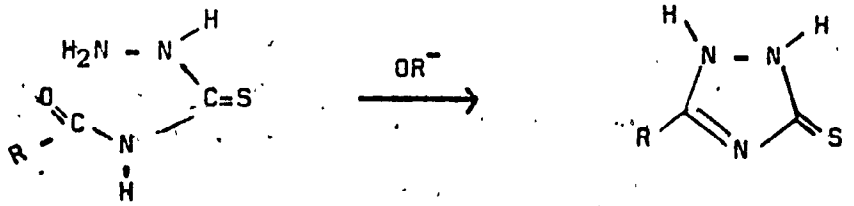
Thiosemicarbazones also readily undergo type A ring closure. For example the thiosemicarbazone of ethyl formate, when treated with a 10 percent sodium carbonate solution for 2 hours at 80°C forms 1,2,4-triazoline-5-thione.[41]



A further example of type A intramolecular condensation is the fusion of certain derivatives of hydrazine N,N'-dithiodicarboxylic acid.[42]



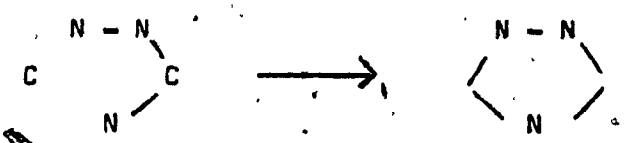
The cyclization of 4-acylthiosemicarbazides in alkaline solution is an example of type B condensation.[4,43]



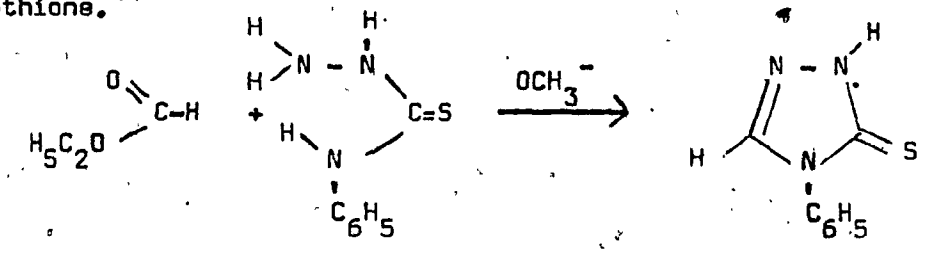
II INTERMOLECULAR CONDENSATION:

Three separate routes are described which have yielded substituted 1,2,4-triazoline-5-thions.

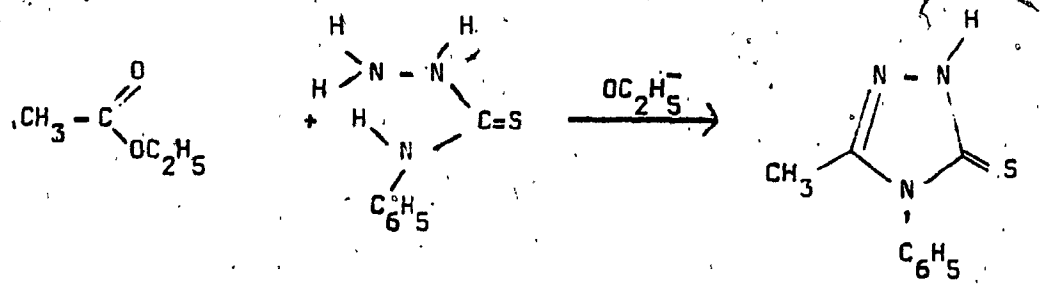
(i)



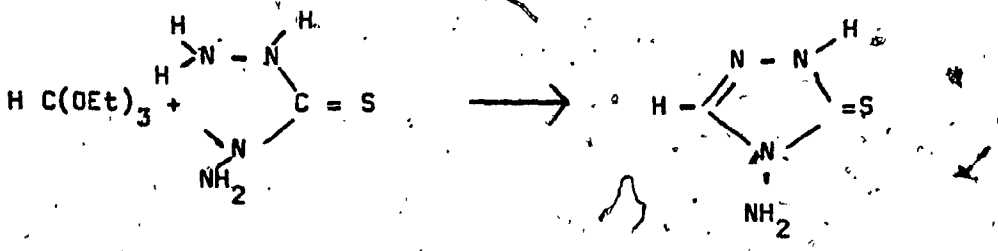
This class is exemplified by the reaction of 4-aryl or 4-alkyl thiosemicarbazides with aliphatic or aromatic acid esters in the presence of base. 4-phenyl thiosemicarbazide reacts with ethyl formate and sodium ethoxide to form 4-phenyl 1,2,4-triazoline-5-thione.[44]



3-substituted, 4-phenyl, 1,2,4-triazoline-5-thione can be prepared by reacting with the appropriate acid ester.[45]



Thiocarbohydrazide reacts with ethyl orthoformate by this route, to produce 4-amino-1,2,4-triazoline-5-thione.[46]



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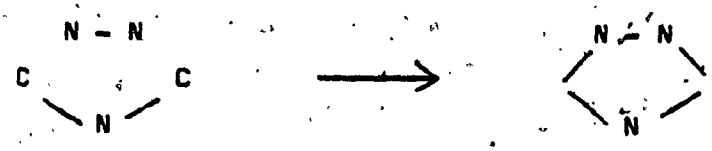
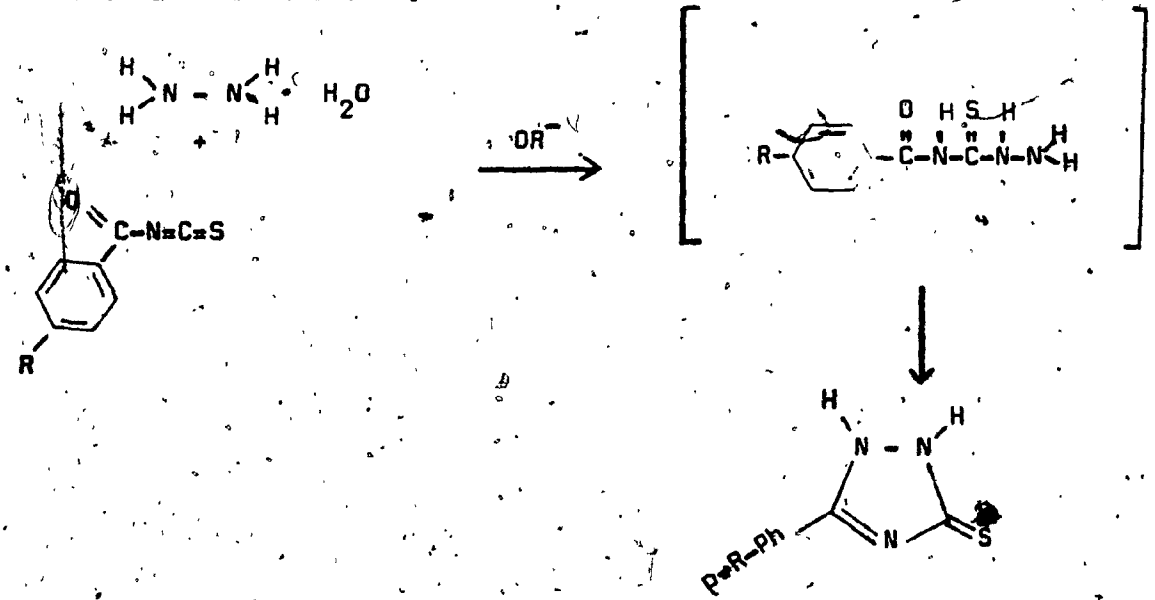
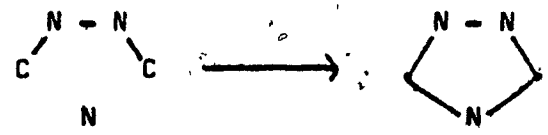
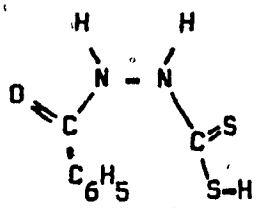


The addition of aroyl isothiocyanate to an excess of hydrazine hydrate under alkaline reaction conditions results in the direct formation of 3-aryl-1,2,4-triazoline-5-thiones in moderate yields (≈ 30%). 4-acyl thiosemicarbazide is expected to be an intermediate in this reaction.[47]

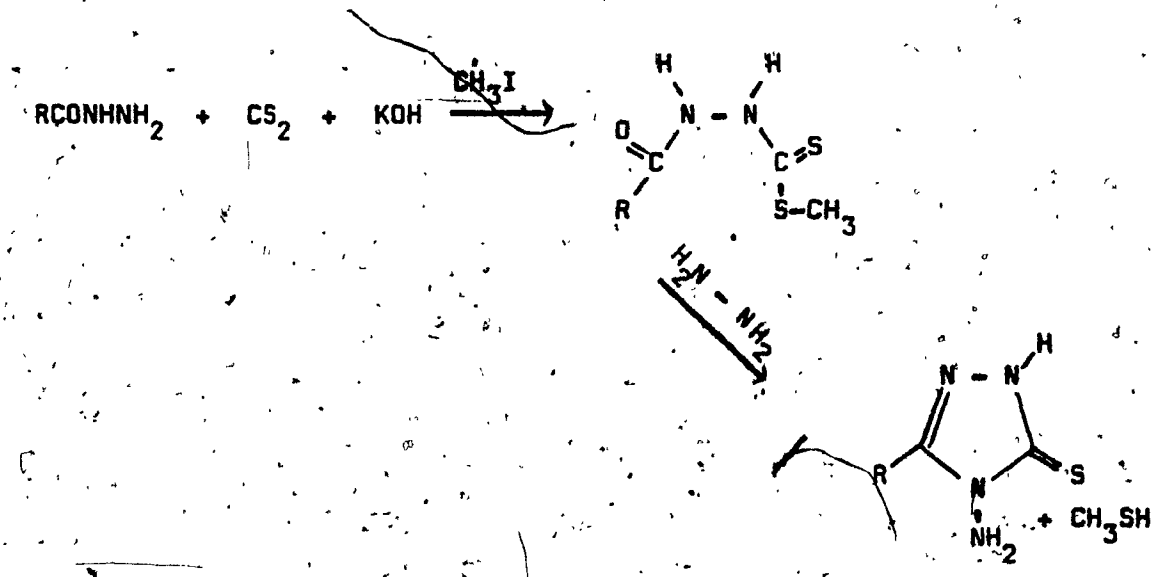


(iii) 

3,4-Disubstituted-5-mercapto triazoles have been obtained via this route from derivatives of N-acylaminodithiocarbamic acids.

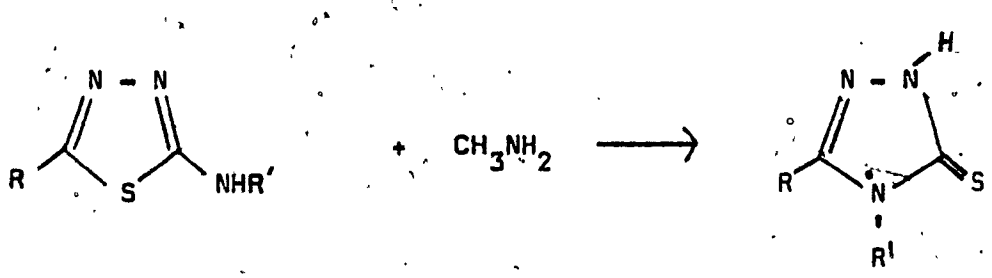


Acylamidodithiocarbamates can be obtained by reacting acyl hydrazides with carbon disulfide and potassium hydroxide, giving the potassium salt of 2-acylthiocarbazic acid. These compounds can be converted into their methyl esters with methyl iodide and they react readily with hydrazine to form the 3,4-disubstituted -5-mercapto triazoles.[48,49]



III REARRANGEMENT OF SUBSTITUTED 1,3,4-THIADIAZOLES

2-Amino-5-substituted, 1,3,4-thiadiazoles, when treated at 150° with methyl amine rearrange to 3,4 disubstituted 1,2,4-triazoline-5-thiones in very good yields.[50]



EXPERIMENTAL

The infra-red spectra were recorded on a Perkin-Elmer 457 Grating Spectrometer using potassium bromide discs and corrected according to a polystyrene standard of 0.05mm in thickness. In this section the main absorption bands are reported for each new compound prepared.

The proton magnetic resonance spectra were obtained on a 60MHz, Varian A-60A instrument. The samples were dissolved in DMSO-d_6, unless otherwise specified, using TMS as internal standard. The chemical shift values were expressed in PPM units from the TMS peak.

Thin-layer chromatograms (TLC) were obtained with silica-gel plates prepared by Eastman Kodak with fluorescent indicator. The solvent system used was:

BENZENE - DIETHYLETHER - CONC. AMMONIUM HYDROXIDE

(20:75:5, V/V/V)

The plates were developed in the above solvent, then the solvent was removed by exposure to atmospheric air and the plates were placed in an atmosphere of iodine vapors.

The melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

The ultra violet spectra were recorded on a Unicam-600 Spectro-photometer, using a slit width of 0.001mm and methanol in the

reference beam. The compounds were dissolved in methanol at a concentration of approximately 0.02g/l.

PREPARATION OF INTERMEDIATES AND PRODUCTS

MONOSUBSTITUTED HYDRAZINES

P-METHOXY PHENYLHYDRAZINE

p-Anisidine (19g, 0.15 moles) was mixed with concentrated hydrochloric acid (150 mL). The mixture was well stirred and diazotized at 0°C with a solution of sodium nitrite (10.4g, 0.15 moles) in water (45mL).

A solution of stannous chloride (105g, 0.55 moles) in water (90 mL) was cooled at 0°C and was slowly added to the purple diazonium solution. A yellow crystalline solid was obtained and turned colourless after standing overnight in the refrigerator. The solid was well drained, washed with diethyl ether, and recrystallized from the minimum amount of boiling water. A solution of sodium hydroxide (3g, 0.075 moles) in water (60 mL) was cooled to 0° and mixed with the recrystallized solid. The resulting free base (4.1g, 18%) was drained well and recrystallized from benzene: mp 62°C - 64°C (lit.[51] 65°C). The compound is unstable both in the free-base form and as the hydrochloride and it begins to decompose within a few hours at room temperature.[56]

P-BROMO PHENYL HYDRAZINE

p-Bromo aniline (34g, 0.20 moles) was mixed with concentrated hydrochloric acid (70 mL) and heated to 60°C for one hour. The mixture was cooled, stirred and diazotized at 0°C with a solution of sodium nitrite (20g, 0.29 moles) in water (50 mL). The diazotization required about 60 minutes. The diazonium solution was filtered and added slowly to a solution of sodium sulphite at 5°C, which had been prepared by passing sulphur dioxide gas into a solution of sodium hydroxide (45g, 1.12 moles) in water (300 mL), until an acid reaction was just indicated by phenolphthalein. The resulting mixture was warmed slowly to 60 °C and maintained at 60° to 70° for one hour. The solution was acidified to litmus with hydrochloric acid and heated on a steam bath for one hour. Concentrated hydrochloric acid (100 mL) was added and the mixture was allowed to cool. The crystals were filtered, washed with 3N hydrochloric acid, then dissolved in hot water (10 liters). The solution was made basic by addition of a solution of 3N potassium hydroxide. The resulting precipitate (14.4g, 39%) was drained well: mp 101-103°C. (lit.[55] 105-107°C).

REACTION OF HYDRAZINES WITH PHENYL ISOTHIOCYANATE

(a) General Low Temperature Procedure:

Absolute ethanol (50 mL) and a magnetic stirrer were added to a 150 mL flask. The hydrazine (0.046 moles) was then dissolved in the ethanol. The flask was placed in an ice-acetone bath and cooled to $-5^{\circ}C$, with constant stirring, phenyl isothiocyanate (6.2g, 0.046 moles) was slowly added dropwise to the mixture so that the reaction temperature did not exceed $-2^{\circ}C$. After stirring for five minutes the resulting precipitate was collected and washed with cold ($-3^{\circ}C$) absolute ethanol. (For specific experimental results see table I.)

(b) General High Temperature Procedure:

Absolute ethanol (50 mL) and a magnetic stirrer were added to a 150 mL flask. The hydrazine (0.046 moles) was then dissolved in the ethanol, and the mixture brought to a reflux with a hot plate. Phenyl isothiocyanate (6.2g, 0.046 moles) was added dropwise to the refluxing mixture. After one hour the solution was cooled and the resulting precipitate was collected and washed with cold absolute ethanol. (See table one for specific experimental results.)

REACTION OF HYDRAZINES WITH METHYL ISOTHIOCYANATE

(a) General Low Temperature Procedure:

Absolute ethanol (25 mL) and a magnetic stirrer were added to a 150 mL flask. The hydrazine (0.024 moles) was then dissolved in the ethanol. The flask was placed in an ice-acetone bath and cooled to $-5^{\circ}C$. Crystals (previously washed with absolute ethanol) of methyl isothiocyanate (1.75g, 0.024 moles) were dissolved in 25 mL of absolute ethanol, then slowly added to the hydrazine solution so that the reaction temperature did not exceed $-2^{\circ}C$. After stirring for five minutes the resulting precipitate was collected and washed with cold ($-3^{\circ}C$) absolute ethanol. (For specific experimental results see table II).

(b) General High Temperature Procedure:

Absolute ethanol (25 mL) was added to a 150 mL flask containing a magnetic stirrer. The hydrazine (0.024 moles) was then dissolved in the ethanol, and the mixture brought to reflux on a hot plate. Crystals (previously washed with absolute ethanol) of methyl isothiocyanate (1.75g, 0.024 moles) were dissolved in absolute ethanol (25 mL), then slowly added to the refluxing hydrazine solution. After one hour the solution was cooled and the resulting precipitate was collected and washed with cold absolute ethanol.

Table III - REACTION OF MONO SUBSTITUTED HYDRAZINES WITH PHENYL ISOTHIOCYANATE

(a) Low Temp. Reaction:

	Reactant Hydrazine	Product Yield (%)	Product mp (°C)	Product TLC (Rf)	Product IR NH_2 deformation frequency (cm^{-1})
(i)	Methyl Hydrazine	52	144-145	0.39	1625
(ii)	Para-methoxy Phenyl hydrazine	42	135-137	0.59	1615
(iii)	Phenyl Hydrazine	82	139-140	0.64 0.48	1625
(iv)	Para-bromo Pheny hydrazine	43	172-174	0.37 0.64	—

(b) High Temp. Reaction:

(i)	Methyl Hydrazine	24	136-138	0.19 0.39	1625
(ii)	Para-methoxy Pheny hydrazine	78	153-154	0.59 0.46	1615
(iii)	Phenyl Hydrazine	81	168-169	0.64 0.48	1625
(iv)	Para-bromo Phenyl hydrazine	65	180-182	0.37	—

Table IV - REACTION OF MONO SUBSTITUTED HYDRAZINES WITH METHYL ISOTHIOCYANATE

(a) Low Temp Reaction:

	Reactant Hydrazine	Product Yield (%)	Product mp (°C)	Product TLC (Rf)	Product IR NH_2 Deformation frequency (cm^{-1})
(i)	Methyl Hydrazine	32	132-135	0.41	1630
(ii)	Para-methoxy Phenyl hydrazine	39	154-157	0.51	1610
(iii)	Phenyl Hydrazine	39	88-90	0.45 0.55	1610
(iv)	Para-bromo Phenyl hydrazine	6	184-186	0.44 0.59	--

(b) High Temp Reaction:

(i)	Methyl Hydrazine	35	132-135	0.41	1630
(ii)	Para-methoxy Phenyl hydrazine	51	146-149	0.42 0.51	1610
(iii)	Phenyl Hydrazine	22	163-165	0.46	--
(iv)	Para-bromo Phenyl hydrazine	39	190-193	0.44	--

ISOMERIZATION OF 2,4,-DISUBSTITUTED-3-THIOSEMICARBAZIDES.

Isomerization of 2-paramethoxy phenyl 4-phenyl-3-thiosemicarbazide.

2-Paramethoxy phenyl-4-phenyl-3-thiosemicarbazide (0.3g, 0.001 moles) was dissolved in absolute ethanol (10 m L), and the solution was then refluxed for 24 hours. Upon cooling and partial evaporation of the solvent, a precipitate formed which was collected by suction filtration and washed with cold absolute ethanol: mp 153-154°C; TLC: (Rf: 0.45).

Isomerization of 2-phenyl-4-methyl-3-thiosemicarbazide.

An approximatly equal mixture of 2-phenyl-4-methyl-3-thiosemicarbazide and 1-phenyl-4-methyl-3-thiosemicarbazide (1.0g, 0.006 moles) was dissolved in absolute ethanol (30 m L), and the solution was refluxed for 24 hours. Upon cooling and partial evaporation of the solvent, a precipitate formed which was collected by suction filtration and washed with cold absolute ethanol: mp 163-165°C; TLC: (Rf: 0.46).

ISOMERIZATION OF 2-PARAMETHOXY PHENYL-3-THIOSEMICARBAZIDE WITH 2-PHENYL-4-METHYL-3-THIOSEMICARBAZIDE.

2-Paramethoxy phenyl-3-thiosemicarbazide (0.5g, .002 moles) and an approximately equal mixture of 2-phenyl-4-methyl-3-thiosemicarbazide and 1-phenyl-4-methyl-3-thiosemicarbazide (1.0g, .006 moles) were dissolved in absolute ethanol (30 mL) and the solution was refluxed for 24 hours. Upon cooling and partial evaporation of the solvent, a precipitate formed which was collected by suction filtration and washed with cold absolute ethanol: TLC: (Rf: 0.46).

THE PREPARATION OF 1-BENZOYLTHIOSEMICARBAZIDE.

1-Benzoylthiosemicarbazide

Powdered thiosemicarbazide (4.6g, 0.051 moles) was suspended in dry pyridine (50 mL) cooled to -5°C, and benzoylchloride (7.0g, 0.050 moles) was added dropwise below 0°C. After 12 hours stirring during which room temperature was attained, water (250 mL) was added, the pyridine removed under reduced pressure, and the oily precipitate was collected and added to boiling water (150 mL). A small amount of charcoal was added to the liquid which was then filtered and allowed to cool, giving colorless leaflets (6.0g, 60%): mp: 193-195°C (lit.[38] 196-198°C).

1-BENZOYL-4-PHENYL THIOSEMICARBAZIDE

4-Phenyl thiosemicarbazide (16.7g, 0.1 moles) was powdered and suspended in dry pyridine (100 mL) cooled to -5°, and benzoyl chloride (14.0g, 0.1 moles) was added dropwise below 0°. After 12 hours of stirring during which room temperature was attained, water (500 mL) was added, the pyridine removed under reduced pressure, and the precipitate (17g, 63%) was collected and recrystallized in ethanol: mp 163-165°C (lit.[38] 166°C).

SUBSTITUTED TRIAZOLINE-5-THIONES

4-Phenyl-1,2,4-Triazoline-5-Thione.

This compound was prepared according to the method of Zotta and Gasmet (2).

After dissolving metallic sodium (2.3g, 0.1 moles) in absolute ethanol (100 mL), 4-phenylthiosemicarbazide (16.7g, 0.1 moles) and ethyl formate (5g, 0.07 moles) were added. The mixture was refluxed for three hours and more ethyl formate (5g, 0.07 moles) was added and the mixture refluxed for another five hours. The solution was evaporated to dryness under vacuum on a rotatory evaporator. The solid residue was dissolved in a solution of sodium hydroxide (2.0g) in water (150 mL) and filtered from a small amount of undissolved material. The filtrate was acidified with acetic acid (3g) in water (30 mL) to precipitate the product which was then filtered, drained well and recrystallized from water (14.2g, 80%): mp 168-170°C (lit.[52] 168-170°C); NMR 7.58 (m,5 H), 8.67 (s, 1 H), 13.8 (s, 1 H).

3-PHENYL-1,2,4-TRIAZOLINE-5-THIONE. - (Method A)

1-Benzoylthiosemicarbazide (3.9g, 0.02 moles) was added to a solution of sodium (1.5g, 0.065 moles) in methanol (50 mL) and the mixture was gently heated under reflux for 12 hours. After evaporation to dryness under reduced pressure, the residue was dissolved in water (100 mL). A small amount of charcoal was added and the solution was filtered then acidified with 10% acetic acid. The product which precipitated (25g, 71%) was filtered, drained well and recrystallized from water: mp 254-255°C (lit.[38] 256°C).

3-PHENYL-1,2,4-TRIAZOLINE-5-THIONE. - (Method B)

Hydrazine hydrate (72.1g, 1.44 moles) was dissolved in ethanol (130 mL). The solution was stirred with a magnetic stirrer and cooled in a water-ice bath. Benzoyl isothiocyanate (33g, 0.20 moles) was added dripwise during five minutes. The temperature rose to 55°C and stirring at room temperature was continued overnight. The clear, pale yellow liquid was evaporated under reduced pressure, the residue diluted with water (200 mL), made strongly acid with 1N HCl and the precipitate was ground in a mortar with 1N HCl (100 mL) and the solid again collected (8.1g, 23%) and washed with water: mp 252-255°C (crystallized from water) (lit.[38] 256°C).

3,4-DIPHENYL-1,2,4-TRIAZOLINE-5-THIONE.

1-Benzoyl-4-phenylthiosemicarbazide (5.4g, 0.02 moles) was added to a solution of sodium (1.5g, 0.065 moles) in methanol (50 mL), and the mixture was gently heated under reflux for 12 hours. After evaporation to dryness under reduced pressure, the residue was dissolved in water (100 mL). A small amount of charcoal was added and the solution was filtered then acidified with 10% acetic acid. The precipitate (2.1g, 42%) was filtered, drained well and recrystallized from ethanol: mp 280-282°C) (lit.[38] 282°C).

4-PHENYL-5-[4'-PHENYL-3'-(1,2,4-TRIAZOLINE-5-THIONES)]-METHYL MERCAPTO 1,2,4-TRIAZOLE.

1-[4'-Phenyl-5'-(1', 2', 4'-triazolyl)] mercapto acetyl-4-phenyl thiosemicarbazide (2.0g, 0.0052 moles) was added to a solution of sodium hydroxide (4.0g, 0.1 moles) in water (50 mL). The mixture was refluxed for one hour then allowed to cool to room temperature. After filtering, the solution was acidified with hydrochloric acid (2.6g, 0.07 moles) in water (70 mL), and the resulting precipitate (1.38g, 73%) was filtered, washed with cold water and aqueous alcohol: mp 180-185°C (crystallized from water); NMR 4.1 (S, 2 H), 7.50 (M, 10 H), 8.83 (S, 1 H), 13.8 (Broad, 1 H).

Anal. Calcd for $C_{17}H_{14}N_6S_2$: C, 55.73; H, 3.82; N, 22.94; S, 17.48. Found: C, 55.52; H, 3.85; N, 22.77; S, 17.48.

TRIAZOLYL-5-MERCAPTO ACETATES

ETHYL (3,4-DIPHENYL-1,2,4-TRIAZOLYL-5) MERCAPTO ACETATE.

This compound was prepared according to the method of Gehlen and Demin (53).

Sodium hydroxide (0.44g, 0.011 moles) was dissolved in an ethanol (20 mL) and water (20 mL) solution. 3,4-Diphenyl-1,2,4-triazoline-5-thione (2.78g, 0.011 moles) was then added to the solution followed by freshly distilled ethyl monochloroacetate (1.38g, 0.011 moles). The reaction was refluxed for four hours and then cooled to room temperature upon which the product precipitated out of solution. The solid material (2.28g, 61%) was then filtered and recrystallized from ethanol: mp 99 - 102°C (lit.[54] 103°C)

ETHYL (3-PHENYL-1,2,4-TRIAZOLYL-5) MERCAPTO ACETATE.

This compound was prepared according to the method of Gehlen and Demin (53).

Sodium hydroxide (0.44g, 0.011 moles) was dissolved in an ethanol (20 mL) and water (20 mL) solution. 3-Phenyl-1,2,4-triazoline-5-thione (2.0g, 0.011 moles) was then added to the solution followed by freshly distilled ethyl monochloroacetate (1.39g, 0.011 moles). The reaction was refluxed for four hours and then cooled to room temperature upon which the product precipitated out of solution. The solid material (2.23g, 77%) was then filtered and recrystallized from ethanol: mp 107 - 109°C.

Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.75; H, 4.97; N, 15.96; S, 12.16. Found: C, 54.57; H, 5.03; N, 15.76, S, 12.03.

ETHYL(4-PHENYL-1;2,4-TRIAZOLYL-5) MERCAPTO ACETATE

This compound was prepared according to a modified method of Gehlen and Osmin (53).

Sodium hydroxide (0.44g, 0.011 moles) was dissolved in an ethanol (20 mL) and water (20 mL) solution. 4-Phenyl-1,2,4-triazoline-5-thione (2.0g, 0.011 moles) was then added to the solution followed by freshly distilled ethyl monochloroacetate (1.39g, 0.011 moles). The reaction was refluxed for 24 hours and after cooling to room temperature was shaken for 15 minutes to precipitate the product (1.71g, 58%) which was then filtered, and recrystallized from a 50% ethanol - water solution: mp 66 - 68°C (lit.[52] 125°C); NMR 1.17 (t, 3 H, J = 7 Hz), 4.09 (s, 2 H), 4.19 (q, 2 H, J = 7 Hz), 7.58 (m, 5 H), 8.88 (s, 1 H).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.75; H, 4.97; N, 15.96; S, 12.16. Found: C, 54.59; H, 5.01; N, 15.78; S, 12.11.

(4-PHENYL-1,2,4-TRIAZOLYL-5) MERCAPTOACETHYDRAZIDE

Ethyl (4-phenyl-1,2,4-triazolyl-5) mercaptoacetate (2.0g, 0.008 moles) and hydrazine hydrate (1.0g, 0.02 moles) were added to absolute ethanol (20 mL). The mixture was refluxed for one hour and upon cooling, a voluminous white precipitate was obtained. The solid material (1.5g, 79%) was then filtered and recrystallized from toluene; mp 152 - 154°C (lit.[52] 153 - 156°C); NMR 3.88 (s, 2 H), 4.30 (broad, 2 H), 7.55 (m, 5 H), 8.83 (s, 1 H), 9.30 (broad, 1 H).

Anal. Calcd. for $C_{10}H_{11}N_5OS$: C, 48.19; H, 4.41; N, 28.11; S, 12.85. Found: C, 48.30; H, 4.60; N, 27.93; S, 12.59.

1- [4'-PHENYL-5'-(1', 2', 4'-TRIAZOLYL)]-MERCAPTOACETYL-4-PHENYL-THIOSEMICARBAZIDE.

(4-Phenyl-1,2,4-triazolyl-5) mercaptoacethydrazide (0.97g, 0.0039 moles) was added to refluxing absolute ethanol (30 mL). Phenyl isothiocyanate (0.53g, 0.0039 moles) was then added dropwise to the boiling reaction mixture which was allowed to boil for a further 15 minutes. The solution was cooled, and the resulting precipitate was filtered and washed with cold absolute ethanol and diethyl ether. The product (1.40g, 93%) was crystallized in absolute ethanol: mp 179 - 181°C; NMR 3.98 (s, 2 H), 7.22 (m, 5 H), 7.57 (m, 5 H), 8.87 (broad, 1 H), 9.67 (broad, 2 H), 10.35 (broad, 1 H).

Anal. Calcd. for $C_{17}H_{16}OS_2$: C, 53.12; H, 4.16; N, 21.87; S, 16.66. Found: C 52.96; H, 3.99; N, 21.62; S, 16.73.

SUBSTITUTED 1,3,4-THIADIAZOLE

4-Phenyl-5-[(5'-Phenyl Amino)-2'-(1,3,4-Thiadiazole)] Methyl Mercapto 1,2,4-Triazole.

1- [4'-Phenyl-5'-(1', 2', 4'-Triazolyl)] mercapto acetyl-4-phenylthiosemicarbazide (2.0g, 0.0052 moles) was slowly added to concentrated sulfuric acid (17 mL) at low temperature (-5 to +5°C). After standing for two Hours the solution was filtered and neutralized at 0°C with a solution of ammonium hydroxide (36g) in water (120 mL). The resulting precipitate (1.5g, 79%) was filtered and washed with cold water: mp 145 - 150°C (crystallized from aqueous methanol); NMR 4.66 (s, 2 H), 7.50 (m, 11 H), 8.93 (s, 3 H).

Anal. Calcd. for $C_{17}H_{16}N_6S_2$: C, 55.73; H, 3.82; N, 22.94; S, 17.48. Found: C, 53.42; H, 3.78; N, 21.83; S, 16.83.

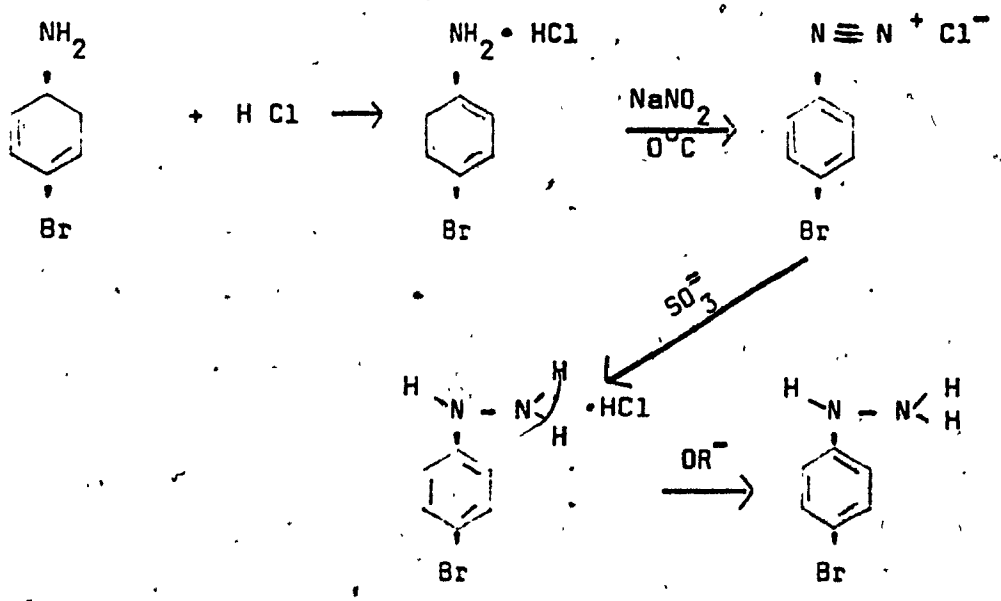
2-AMINO-5-PHENYL-1,3,4-THIADIAZOLE.

1-Benzoyl thiosemicarbazide (2.0g, 0.010 moles) was added to a solution of concentrated sulfuric acid and water (40 mL 50/50), during 10 minutes. The beaker containing the reaction mixture was immersed in an oil-bath maintained at 120°C, and kept there for 30 minutes with continual stirring. The solution was then cooled and diluted with water to 100 mL. The addition of excess ammonia solution formed a precipitate. The product (1.2g, 70%) was recrystallized from aqueous alcohol (25% water) giving colourless square plates: mp 219 - 221°C (lit.[38] 224°C).

DISCUSSION

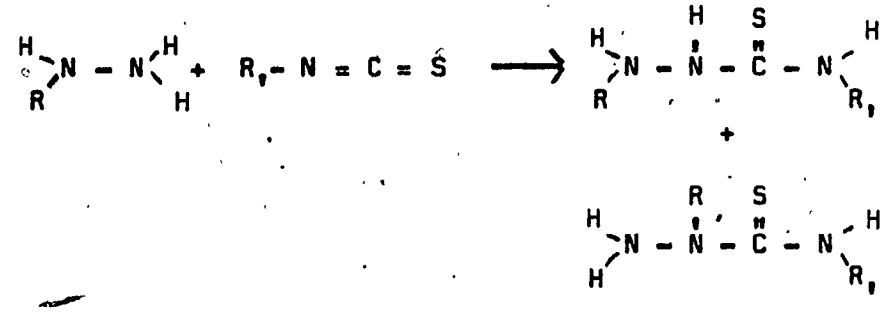
The Reaction Sequence and Mechanistic Routes Leading To The Intermediates And Products.

Intermolecular and intramolecular condensation reactions involving thiosemicarbazides and their derivatives are major synthetic pathways used to produce substituted triazoline-5-thiones. Our initial aim was to investigate the reaction of mono substituted hydrazines with alkyl and aryl isothiocyanates to form substituted thiosemicarbazides. The aryl hydrazines used in this work were either commercially available or prepared by the reduction of their corresponding diazonium salts[57]. For example the preparation of para-bromophenylhydrazine was as follows:

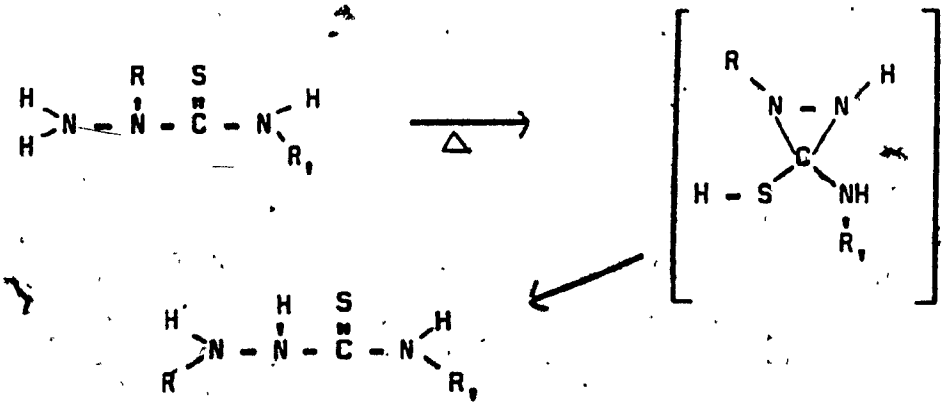


Scheme 1. The Preparation of para-Bromophenylhydrazine.

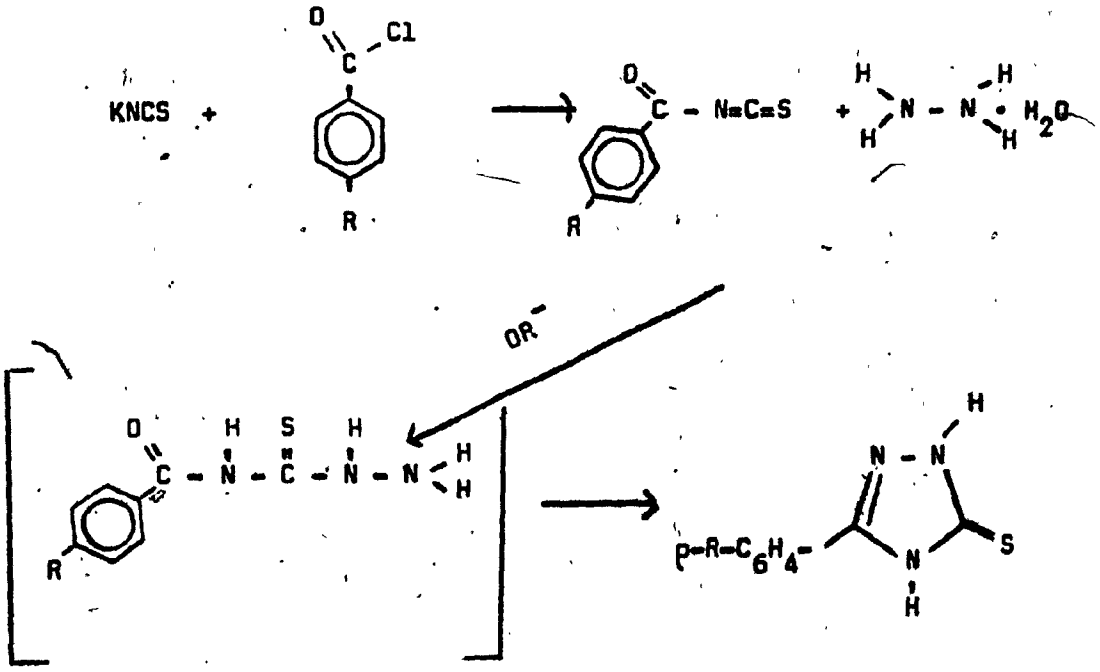
Methyl hydrazine, the only alkyl hydrazine used was commercially available. The mono substituted hydrazines were reacted with alkyl and aryl isothiocyanates in refluxing ethanol (78°C) and at low (-5°C) temperatures to produce 1,4 and/or 2,4-disubstituted thiosemicarbazides. Which one of the two isomeric thiosemicarbazides was formed, was found to depend on both the reaction temperature and the substituent on the hydrazine molecule.



Several of the 2,4-disubstituted thiosemicarbazides, on heating, were found to isomerize to 1,4-disubstituted compounds, possibly through an intramolecular diaziridine type mechanism.

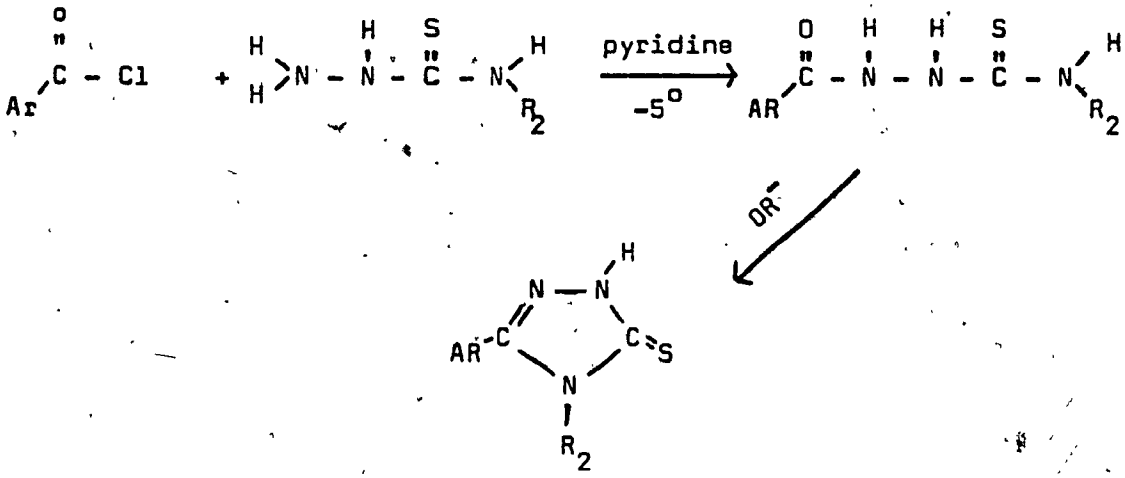


Our further aims in this project were to prepare substituted 1,2,4-triazoline-5-thiones, and with these compounds as possible starting material, to devise a synthetic route leading to the formation of novel bis 1,2,4-triazole type compounds. Three routes were utilized for the preparation of substituted 1,2,4-triazoline-5-thiones. The first involved the reaction of an aroyl isothiocyanate with an excess of hydrazine hydrate under alkaline conditions. The aroyl isothiocyanate was prepared by the action of potassium thiocyanate on the appropriate aroyl chloride.



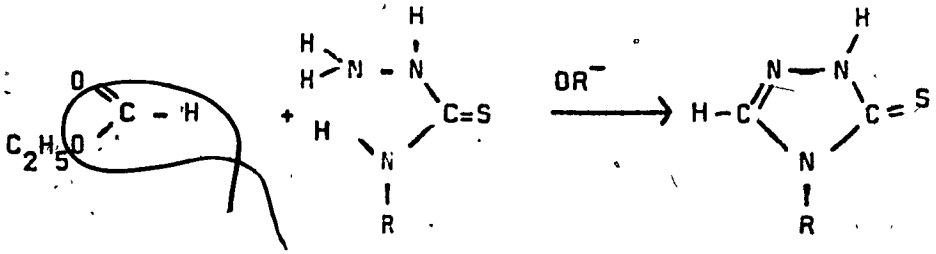
Scheme 2. Synthetic Route - 1, Leading to Substituted 1,2,4-Triazoline-5-Thiones.

The second route involved the benzoylation of 4-substituted thiosemicarbazide followed by cyclization in base to give 3,4-disubstituted 1,2,4-triazoline-5-thiones.



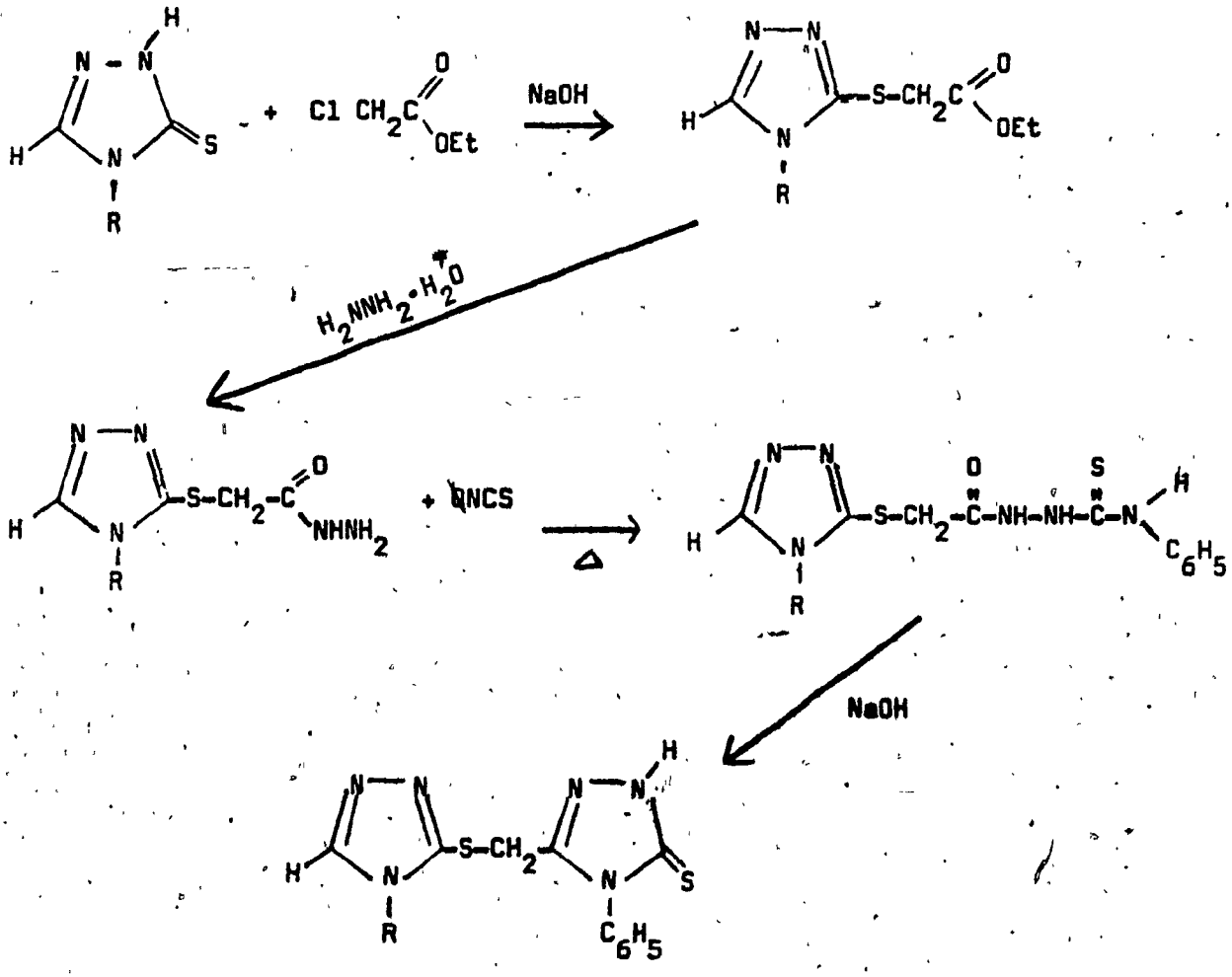
Scheme 3. Synthetic Route - 2, Leeding to Substituted 1,2,4-Triazoline-5-Thiones.

The intermolecular condensation of 4 substituted thiosemicarbazides with ethyl formate in the presence of base is the third synthetic route. It was used to produce 4-substituted 1,2,4-triazoline-5-thiones.



Scheme 4. Synthetic route -3, Leading to Substituted 1,2,4-Triazoline-5-Thiones.

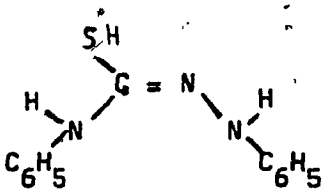
The reaction sequence leading to the novel bis 1,2,4-triazole type compounds involved alkylation of the substituted 1,2,4-triazoline-5-thione with ethyl monochloroacetate to yield the corresponding S-substituted ester derivative, obtaining the hydrazide of this compound by reacting it with hydrazine hydrate and condensing the hydrazide with an aryl isothiocyanate to give a substituted 1-acetyl-4-aryl thiosemicarbazide which on cyclization with base yielded the novel end product.



Scheme 5. Reaction Sequence Leading to bis 1,2,4-Triazole Type Compounds.

THE REACTION OF ISOTHIOCYANATES WITH MONO SUBSTITUTED HYDRAZINES

This reaction was initially examined in the 1890's by W. Marckwald who concluded that phenylisothiocyanate reacted with phenyl hydrazine to yield two isomeric thiosemicarbazides of the following structure.[58]



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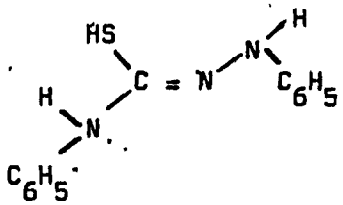
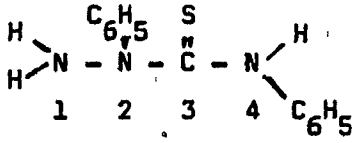
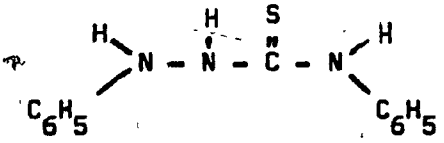


SYN.

This was subsequently corrected by M. Busch and H. Holzmann who proposed the 2,4 and 1,4 diphenyl thiosemicarbazide isomers.[59]



2,4-diphenyl thiosemicarbazide.



1,4-diphenyl thiosemicarbazide

Busch later investigated the reaction of several monosubstituted aryl hydrazines with phenyl and methyl isothiocyanate under various reaction conditions. He found that at low reaction temperature (0^{o}) the major product formed was the 2,4,-disubstituted isomer and conversly at high reaction temperatures,

the 1,4-disubstituted isomer was the major product formed. Busch also found that the 2,4-disubstituted isomers could be isomerized into the more thermally stable 1,4-isomers in most cases only by prolonged heating of the isomers above their melting point.[60,61] More recently, K.A. Jensen, working with alkyl hydrazines concluded that the reaction of monoalkylhydrazines with various substituted isothiocyanates at room temperature, always yields 2,4-dialkylthiosemicarbazides as the primary product, and that the substituent on the isothiocyanate seemed to be almost without influence on the course of the reaction.[62]

THE REACTION OF ISOTHIOCYANATES WITH HYDRAZINES.

The reaction was carried out in absolute ethanol at two separate temperatures. In the first case the isothiocyanate was added dropwise to a solution of the hydrazine maintained at approximately -5^{o}, whereas in the second case the isothiocyanate was added dropwise to the refluxing hydrazine solution.

$$H_2N\text{-}NHR + R_1\text{-}NCS \xrightarrow[(1)\ -5^{o}\quad (2)\ 79^{o}]{\text{absolute ethanol}} H_2N - \overset{R}{\overset{|}{N}} - \overset{S}{\overset{\|}{C}} - NHR_1$$

2,4-disubstituted thiosemicarbazide.

+

$$RNH - NH - \overset{S}{\overset{\|}{C}} - NHR_1$$

1,4-disubstituted thiosemicarbazide.

The results of the reaction carried out at -5^{o} are summarized in table V, and those for the reaction carried out at 79^{o} are summarized in table VI. For purpose of this discussion, the alky or aryl substituted nitrogen atom of the hydrazine molecule will be referred to as the β-nitrogen.

$$\underset{\alpha}{H_2N} - \underset{\beta}{NHR}$$

TABLE V — RESULTS OF THE REACTIONS OF ISOTHIOCYANATES WITH HYDRAZINES AT ~ -5°

R	R_1	Product mp °C	Total Product Yield %	$H_2N-N(R)-C(=S)-NHR_1$	$RNH-NH-C(=S)-NHR_1$	Literature mp of 2,4 Isomer °C
CH_3	C_6H_5	144–145	52	Only Product	——	146 – 147 [62]
p-$OCH_3(C_6H_4)$	C_6H_5	135–137	42	Only Product	——	New Compound
C_6H_5	C_6H_5	139–140	82	Mixture	Mixture	138 [58]
p-$Br(C_6H_4)$	C_6H_5	172–174	43	Minor Product	Major Product	160 [64]
CH_3	CH_3	132–135	32	Only Product	——	136 – 137 [62]
p-$OCH_3(C_6H_4)$	CH_3	154–157	39	Only Product	——	
C_6H_5	CH_3	88–90	39	Mixture	Mixture	90 – 91 [62]
p-$Br(C_6H_4)$	CH_3	184–186	6	Minor Product	Major Product	133 [58]

TABLE VI

RESULTS OF THE REACTIONS OF ISOTHIOCYANATES WITH HYDRAZINES AT 79°

R	R_1	Product mp °C	Total Product Yield %	$H_2N-N-\overset{R}{\underset{|}{}}-\overset{S}{\underset{\|}{C}}-NHR_1$	$RNH-NH-\overset{S}{\underset{\|}{C}}-NHR_1$	Literature mp of 1,4 Isomer °C
CH_3	C_6H_5	136–138	24	Major Product	Minor Product	99 – 100[62]
p-$OCH_3(C_6H_4)$	C_6H_5	153–154	78	Mixture	Mixture	160[63]
C_6H_5	C_6H_5	168–169	81	Minor Product	Major Product	176[58]
p-$Br(C_6H_4)$	C_6H_5	180–182	65	——	Only Product	200[64]
CH_3	CH_3	132–135	35	Only Product	——	135 – 136[62]
p-$OCH_3(C_6H_4)$	CH_3	146–149	51	Mixture	Mixture	
C_6H_5	CH_3	163–165	22	——	Only Product	169 – 170[62]
p-$Br(C_6H_4)$	CH_3	190–193	39	——	Only Product	199[58]

Analogous to isocyanates, the reactions and reactivity of isothiocyanates can be understood by considering the electronic structure of the isothiocyanate group and the effect on this structure of various groups attached to the nitrogen atom.

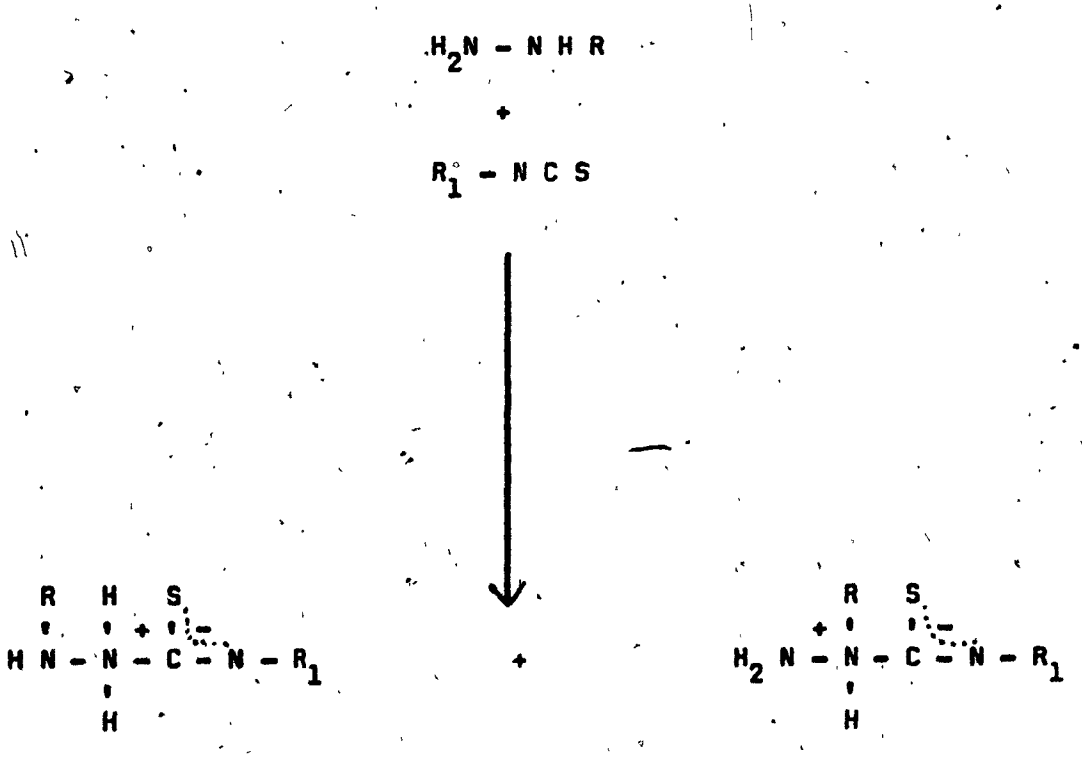
The valence bond resonance structures of isothiocyanate can be represented as follows:

$$R - \overset{-}{N} - \overset{+}{C} = S \longleftrightarrow R - N = C = S \longleftrightarrow R - N = \overset{+}{C} - \overset{-}{S}$$

Minor Major

Potential nucleophiles such as one of the nitrogen atoms of a mono substituted hydrazine molecule will add to the carbon atom of the polarized azomethane linkage of the isothiocyanate group. Neglecting steric factors, any electron withdrawing group attached to the isothiocyanate will increase the positive charge on the carbon atom, and thus increase the reactivity of the isocyanate toward nucleophilic attack. In the same manner any electron withdrawing group attached to one of the nucleophilic nitrogen atom of a hydrazine molecule will decrease the nucleophilic character of the nitrogen atom it is attached to and hence its reactivity towards the azomethane linkage of the isothiocyanate group. This is demonstrated in table V

where it can be seen that the greater the electron withdrawing group on the nitrogen atom of the hydrazine, the less involved it is in reaction with the isothiocyanate to form the 2,4-disubstituted thiosemicarbazide. This may be summarized as follows:



P-Br (C_6H_4) > C_6H_5 > $POCH_3$ (C_6H_4) > CH_3

Electron withdrawing.
Inductive
Effect

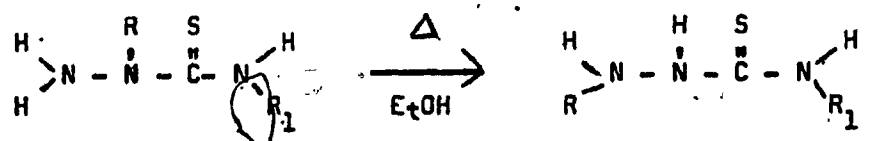
Scheme 6. The Effect of R-Substituents on The Condensation of Isothiocyanates with Monosubstituted Hydrazines.

Both intermediates rearrange by a proton migration to the final products. The same effect is evident in table VI which summarizes the reaction performed at 79°, although somewhat more of the 1,4-isomer was formed here. It can also be seen from tables V and VI that the substituent on the isothiocyanate whether alkyl or aryl exhibited little effect on the resulting thiosemicarbazide product distribution.

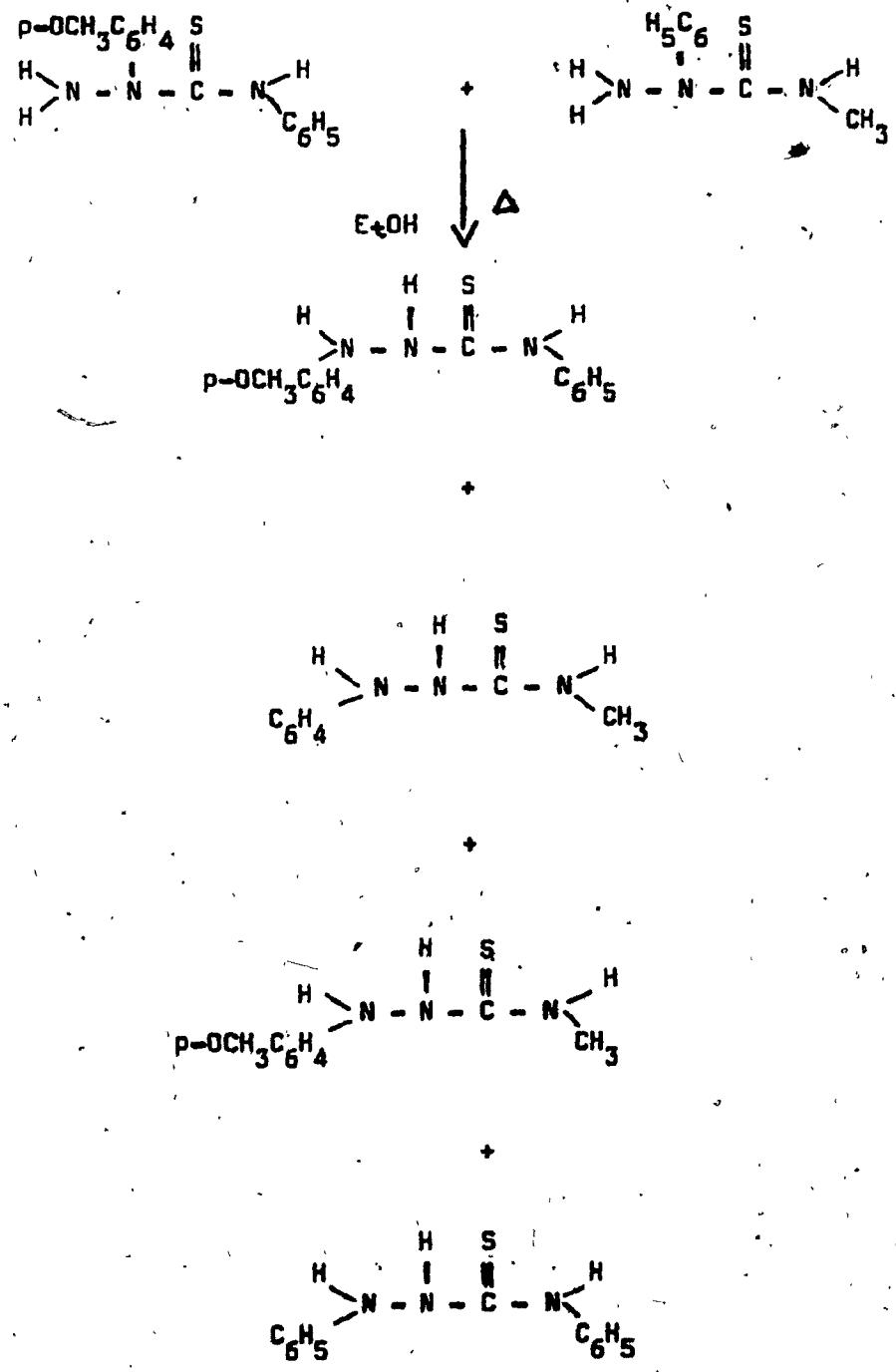
Separation and qualitative evaluation of the reaction products was accomplished with thin layer chromatography, while the constitution of an isomer was determined from literature melting point values and from infrared analysis since only the 2,4-isomer shows an NH_2 deformation band in the 1600 - 1650 Cm^{-1} region.

THE ISOMERIZATION OF SOME 2,4 DISUBSTITUTED THIOSEMICARBAZIDES.

The 2-para-methoxy -4-phenyl thiosemicarbazide, and the mixture of 2,4- and 1,4- isomeric products obtained from the reaction of methyl isothiocyanate with phenyl hydrazine, were dissolved in absolute ethanol and refluxed for 24 hours. Under these conditions, the 2,4-disubstituted thiosemicarbazides isomerized to the more thermally stable 1,4-isomers.

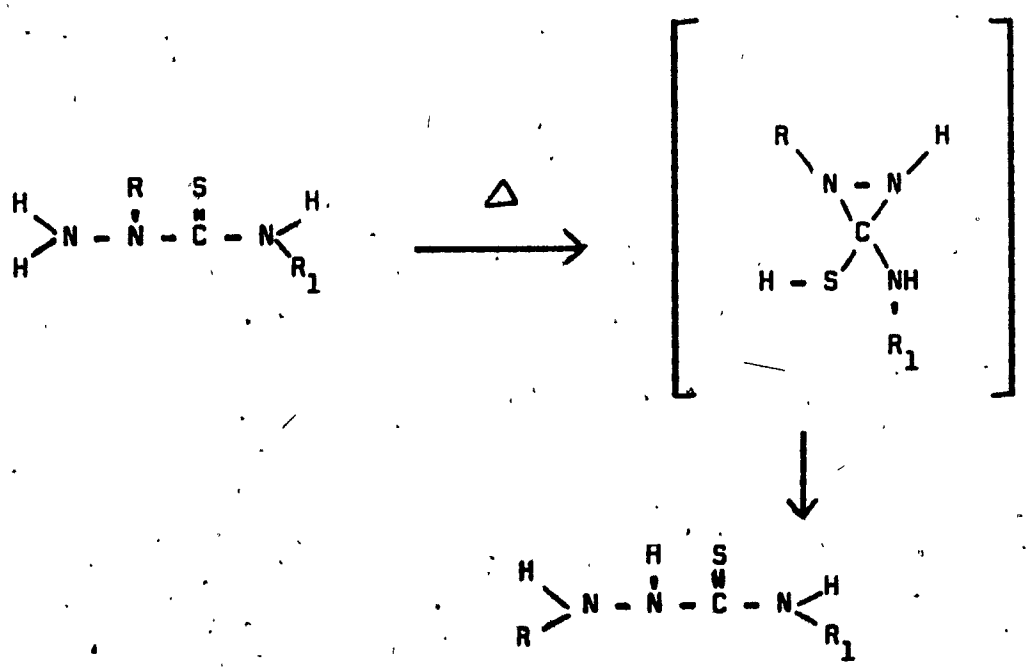


The above mentioned two thiosemicarbazides were then isomerized together under the same reaction conditions. If the isomerization occurs by an intermolecular pathway, such as the breaking up of the compound into a substituted hydrazine and a substituted isothiocyanate and then recombining again into the thermally favoured isomer, then the following four products would be expected:



Scheme 7. Possible isomerization products of a Pair 2,4-Disubstituted Thiosemicarbazides.

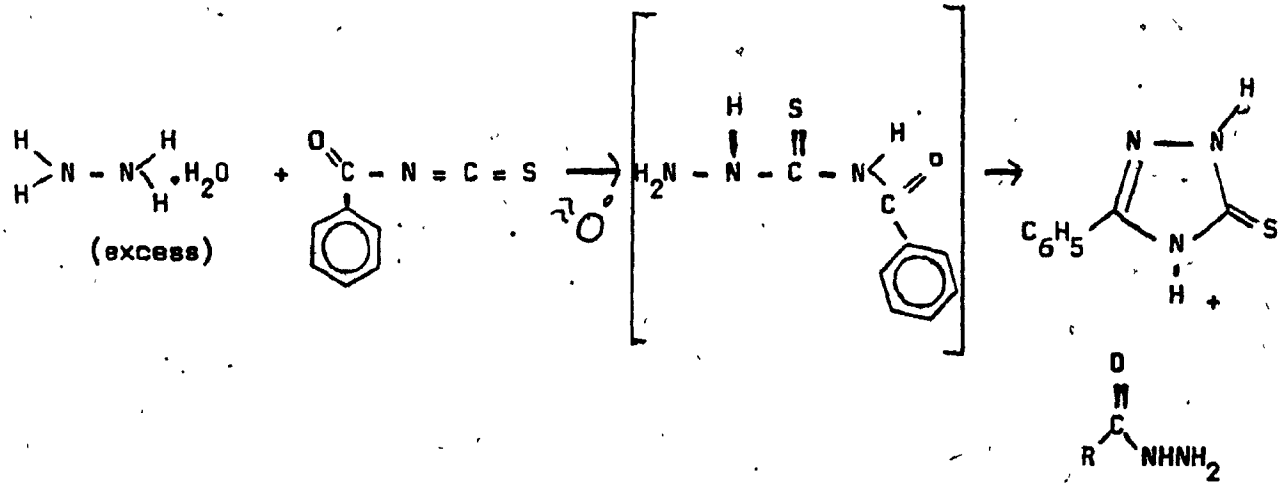
As determined by thin layer chromatography, no 1-paramethoxy-4-methyl thiosemicarbazide was formed by this reaction. The R_f values of the other three 1,4-disubstituted compounds were too similar to conclude that 1,4-diphenyl thiosemicarbazide was not present as well. Since this evidence favors an intramolecular isomerization process, the following intramolecular diaziridine type mechanism is proposed.



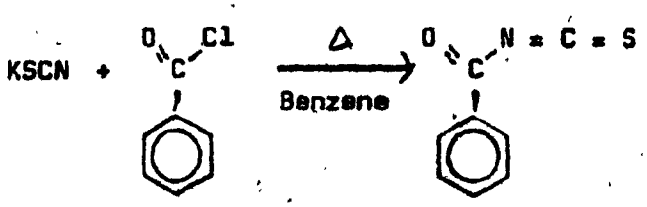
THE PREPARATION OF SUBSTITUTED 1,2,4-TRIAZOLINE-5-THIONE'S

I. The Reaction Of Hydrazines With Aroyl Isothiocyanates.

Benzoyl isothiocyanate has been shown to react with phenylhydrazine to give mainly 4-benzoyl-1-phenylthiosemicarbazide.[65] More recently it has been found that if the isothiocyanate was dropped into an excess of hydrazine, a mixture of 3-phenyl-1,2,4-triazoline-5-thione and benzoyl hydrazide was formed.[47]



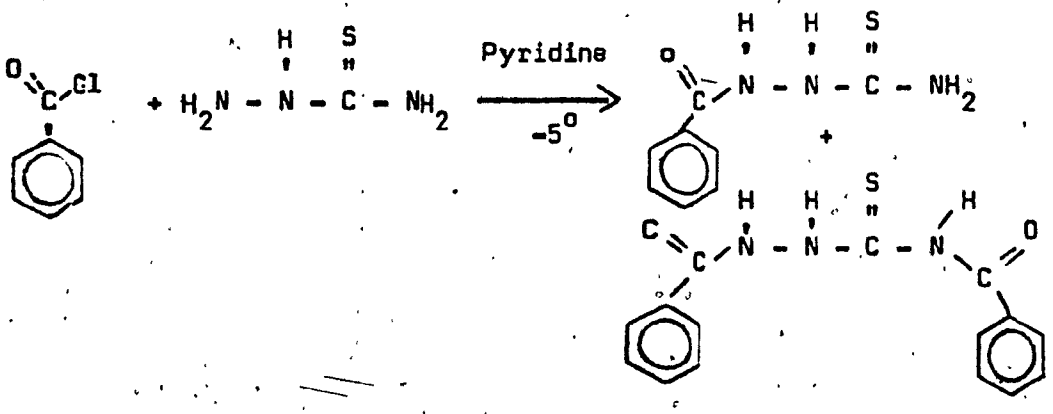
Presumably 4-benzoyl thiosemicarbazide is formed first and then spontaneously cyclises with loss of water. This method was initially utilized to produce 3-phenyl-1,2,4-triazoline-5-thione. The benzoylisothiocyanate was prepared by refluxing potassium thiocyanate with benzoyl chloride in dry benzene.[66]



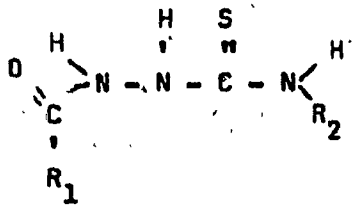
The yield of 3-phenyl 1,2,4-triazoline-5-thione obtained by this procedure was only 23%. This drawback prompted the search for alternate routes for preparing 3 substituted 1,2,4-triazoline-5-thiones.

II The Cyclization of 1-Benzoyl Thiosemicarbazides.

Originally Marckwald and Bott, as well as Oates and Younge prepared 1-benzoyl derivatives of 4-aryl and 4-alkyl thiosemicarbazides by reaction of benzoyl hydrazide with aryl and alkyl isothiocyanates.[67,68] Hoggarth has prepared 1-benzoylthiosemicarbazide by three separate routes: By the reaction of benzoylhydrazide with ammonium thiocyanate, by cautiously heating thiosemicarbazide with the theoretical amount of benzoyl chloride, and by benzoylation in ice-cold pyridine.[38] The latter route was found to be the most convenient, even though small quantities of 1,4-dibenzoylthiosemicarbizide were obtained. Due to differences in their solubilities, the two products were easily separated.



This method was employed to prepare the following 1,4-di-substituted thiosemicarbazides.

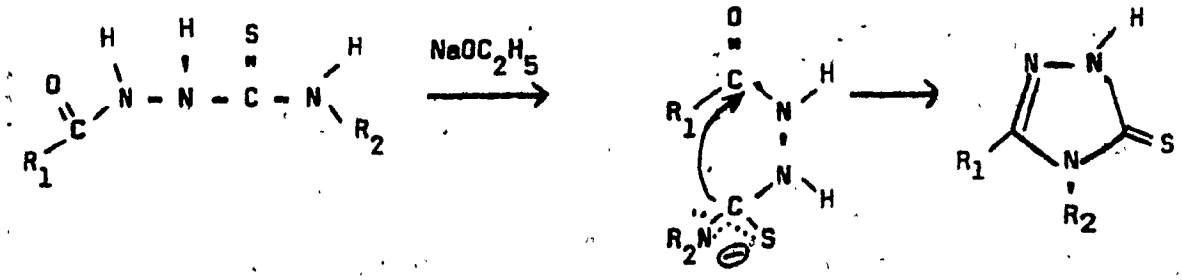


(1) R_1 = Phenyl and R_2 = H

(2) R_1 = Phenyl and R_2 = Phenyl

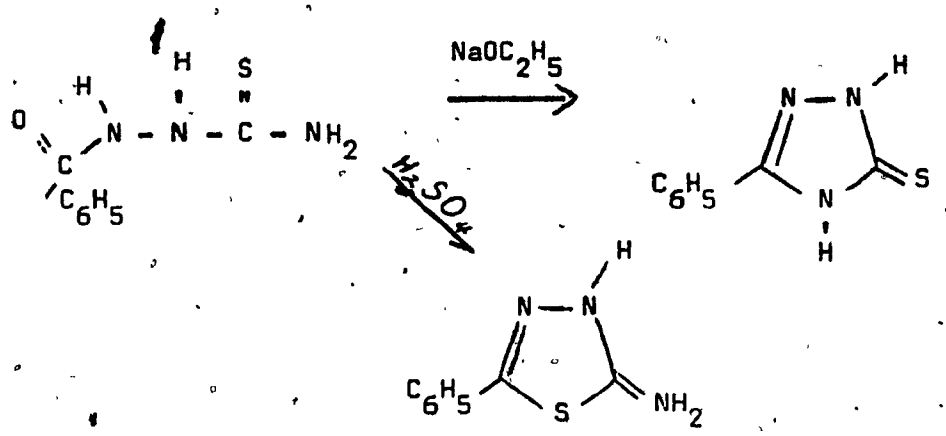
(3) R_1 = 3,5 dinitrophenyl and R_2 = H

The 1-benzoythiosemicarbazides were boiled in alcoholic sodium ethoxide to form, with the elimination of water, the following substituted 1,2,4-triazoline-5-thiones:



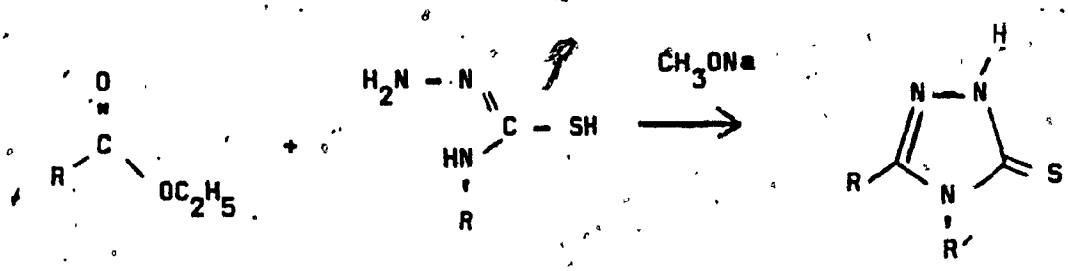
R_1	R_2	Yield
Phenyl	H	71%
Phenyl	Phenyl	42%
3,5-dinitro Phenyl	H	—

Only a black tarry product was obtained when cyclization of 1-(3,5 dinitro benzoyl) thiosemicarbazide was attempted. In contrast to the foregoing, benzoyl thiosemicarbazide was also refluxed in an acidic media to give 2-amino-5-phenyl 1,3,4-thiadiazole. The importance of dehydrating 1-benzoyl-thiosemicarbazide under alkaline conditions to obtain triazoline-thiones was originally expounded by Hoggarth.[38]



III The Reaction Of Aliphatic Acid Esters With 4-Substituted Thiosemicarbazides.

Certain mono- and di-substituted 5-mercaptotriazole derivatives have been synthesized in very good yields by direct condensation of aliphatic acid esters with substituted 4-thiosemicarbazides in the presence of alkaline agents.[52]

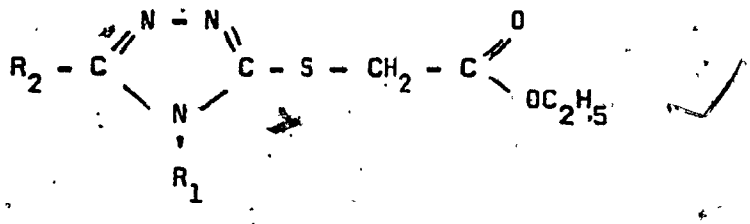


In this manner, ethyl formate was reacted with 4-phenyl thiosemicarbazide to produce 4-phenyl-1,2,4-triazoline-5-thione in 80% yield.

PREPARATION OF S-SUBSTITUTED ESTER DERIVATIVES OF 1,2,4-TRIAZOLINE-5-THIONES.

Initially attempts to prepare S-substituted ester derivatives, according to a procedure followed by V. Zolta and A. Gamet, were unsuccessful. This method involved dissolving the parent triazole in acetone and adding ethyl monochloroacetate to the refluxing solution.[52] After 4 hours of refluxing, only the starting material was obtained.

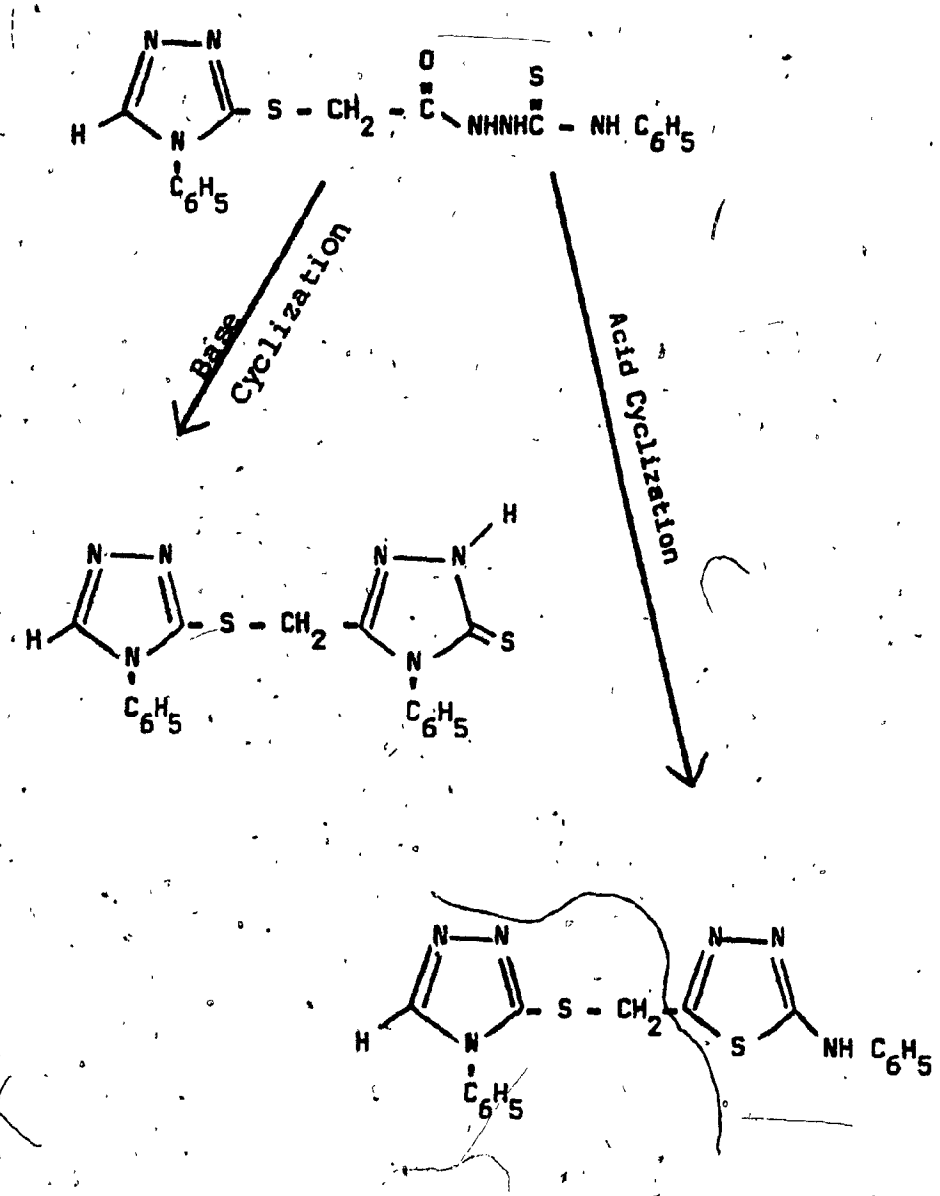
The following substituted ethyl (1,2,4-triazolyl-5) mercaptoacetates were prepared, by refluxing the parent 1,2,4-triazoline-5-thiones with monochloroacetate in the presence of sodium hydroxide. This procedure was utilized by H. Gehlen and P. Oemin.[53]



			Ester carbonyl absorption freq. Cm^{-1}
(1)	R_2 = Phenyl, R_1 = H	Yield: 77%	1720 (s)
(2)	R_2 = Phenyl, R_1 = Phenyl	Yield: 61%	1730 (s)
(3)	R_2 = H R_1 = Phenyl	Yield: 58%	1730 (s)

SYNTHESIS OF 4-PHENYL-5 [4'-PHENYL-3'-(1,2,4-TRIAZOLINE-5-THIONE)] METHYLMERCAPTO- 1,2,4-TRIAZOLE AND 4-PHENYL-5- [5'-PHENYL AMINO) -2' (1,3,4,-THIADIAZOLE)] METHYLMERCAPTO -1,2,4-TRIAZOLE.

As depicted in scheme 5 , ethyl-(4-phenyl-1,2,4-triazolyl-5) mercapto acetate was reacted with hydrazine hydrate to give the hydrazide derivative which was condensed with phenyl isothiocyanate to yield the substituted 1-acetyl-4-phenyl thiosemicarbazide which on cyclization under the influence of alkali, formed 4-phenyl-5 [4'-phenyl-3'-(1,2,4-triazoline-5-thione)] methylmercapto - 1,2,4-triazole. The IR spectra of this compound contained an absorption frequency at 1325 Cm^{-1}, probably due to the thiocarbonyl stretching vibration. When the substituted 1-acetyl-4-phenyl thiosemicarbazide was cyclized under the influence of acid, the result was the formation of 4-phenyl-5- [5'-phenyl amino) -2'(1,3,4-thiadiazol)] methylmercapto-1,2,4-triazole.



Scheme 8. Acid and Base Cyclization of 1-[4' Phenyl-5'(1',2',4'-Triazolyl)]Mercaptoacetyl-4-Phenyl Thiosemicarbazide.

SPECTROSCOPIC STUDIES

ULTRA-VIOLET SPECTRA

The ultra violet spectra were recorded on a Unicam - 600 Spectrophotometer, using a slit width of 0.001 mm, and methanol in the reference beam. The organic compounds were dissolved in methanol at a concentration of about 0.02 g/l. Tables VII, VIII and IX summarize the spectra of substituted 1,2,4-triazoline-5-thiones, S-substituted ester derivatives of 1,2,4-triazoline-5-thiones, and 2,5 disubstituted 1,3,4-thiadiazoles.

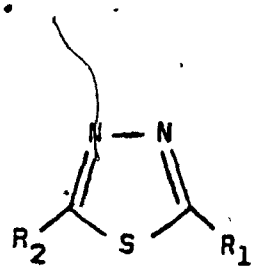
UV Spectroscopy has been used to differentitate between N and S substituted derivatives of 1,2,4-triazoline-5-thiones. The spectra of the N-derivatives are similar to those of the starting thione, whereas the S-derivatives are not.[19]

Lawson and Morley have shown that S-methyl derivatives of 2-mercapto-benzothiazole absorb at lower wavelengths, with a great reduction in intensity.[69] By comparing the data in tables VIII and IX, it can be seen that the S-substituted ester derivatives prepared, absorb at lower wavelengths than their parent compounds, indicating that the alkylation has occurred on the sulfur atom.

The UV spectra of 1,2,4-triazoline-5-thiones and their isomeric 1,3,4-thiadiazoles are very different and serve as a basis for distinguishing these compounds.[70]

G.A. Reynolds and J.A. Van Allan have found that 1,3,4-thiadiazole compounds exhibit an absorption peak at longer wave lengths than their isomeric 1,2,4-triazoline-5-thione derivatives.[70] A comparison of the data in tables VIII and IX shows that the 2,5-disubstituted 1,3,4-thiadiazoles exhibit a large absorption peak at approximately 300 (NM) which does not exist in their isomeric 1,2,4-triazoline-5-thiones.

Table VII Ultra-Violet Spectra Data of 2,5-Disubstituted-1,3,4-Thiadiazoles.



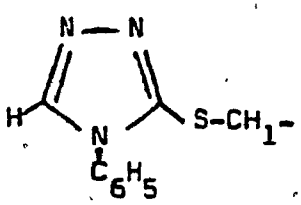
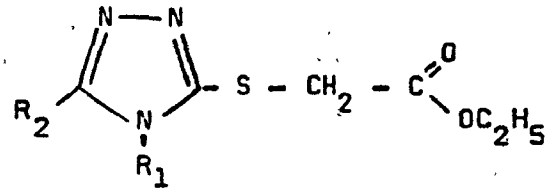
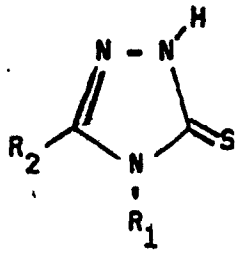
R_1	R_2	Wavelength (nm)[a]	Molar Extinction Coefficient, $\epsilon \times 10^{-3}$	Log ϵ
$-NH_2$	Phenyl	210	6.2	3.8
		220 (SH)	5.3	3.7
		301	12.5	4.1
$-NH-C_6H_5$		211	14.4	4.2
		243 (SH)	8.0	3.9
		302	12.9	4.1

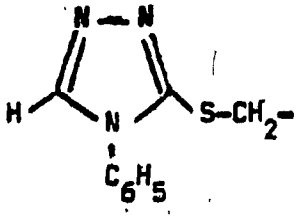
Table VIII Ultra-Violet Spectra Data of S-substituted Ester Derivatives of 1,2,4-Triazoline - 5 - thiones.



R_1	R_2	Wave Length (nm)[a]	Molar Extinction Coefficient, $\varepsilon \times 10^{-3}$	Log ε
H	Phenyl	211	9.7	4.0
		235	12.2	4.1
		255 (SH)	9.6	4.0
Phenyl	Phenyl	213	15.8	4.2
		260	13.3	4.1
Phenyl	H	212	8.1	3.9
		250 (SH)	3.0	3.5

Table IX Ultra-Violet Spectra Data Of 1,2,4-Triazoline-5-Thione Derivatives.



R_1	R_2	Wavelength (nm)[a]	Molar Extinction Coefficient, $\epsilon \times 10^{-3}$	Log ϵ
H	Phenyl	225	11.4	4.1
		257	15.2	4.2
		280 (SH)	9.3	4.0
Phenyl	Phenyl	214	12.5	4.1
		235 (SH)	11.2	4.0
		264	11.4	4.1
Phenyl	H	216	9.2	4.0
		266	7.8	3.9
Phenyl		213	15.5	4.2
		259	11.6	4.1

INFRARED SPECTRA

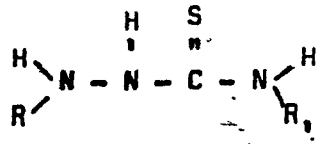
The infrared spectra were recorded on a Perkin-Elmer 457 Spectrometer using potassium bromide discs and corrected according to a polystyrene standard of 0.05 mm in thickness. The data of the thiosemicarbazides and triazoline thiones are discussed whereas fundamental assignments of various other products synthesized are included in the general discussion and experimental section of the thesis.

With respect to 1,4- and 2,4-disubstituted thiosemicarbazides, the constitution of an isomer is evident from its I.R. spectrum, since only the 2,4-isomer shows an NH_2 deformation band in the 1650 - 1600 Cm^{-1} region.[62] Also, as with primary amines, the 2,4 isomers show two absorption bands in the NH stretching region, 3500 - 3300 Cm^{-1}, whereas the 1,4-isomers, like secondary amines, show only one NH stretching band in this area.[71] These differences are depicted in tables IX and X respectively, for the pure 2,4- and 1,4-disubstuted thiosemicarbazides produced in this study.

Infrared spectroscopy has been used to determine the principal thione - thiol tautomeric form present, in the solid state, of triazoline thiones. Three distinguishing features in the IR spectrum have been utilized. The presence or absence

of (i) S–H stretching frequencies in the 2550 - 2600 Cm^{-1} region.[45] (ii) N–H stretching bands located in the 3160 - 3190 Cm^{-1} region[17] (iii) and thiocarbonyl stretching vibrations of the thioamide form, $\geq N - C = S$, around 1300 Cm^{-1}.[45] This IR data is tabulated in table XII for the various triazoline thiones produced. The absence, in all cases, of S–H stretching frequencies, and the presence of broad absorption bands in the 2920 - 3300 Cm^{-1} range which could in part be due to N - H stretching, as well as the presence of bands in the 1300 Cm^{-1} region, indicate that these compounds are present, in the solid state, in the thione tautomeric form.

TABLE X SIGNIFICANT IR FREQUENCIES IN THE SPECTRA OF 1,4 DISUBSTITUTED THIOSEMICARBAZIDES.



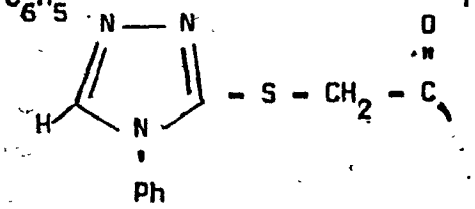
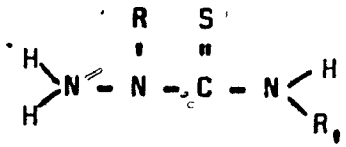
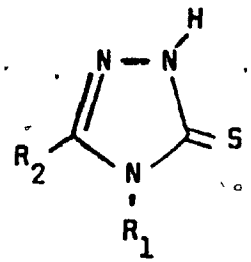
R	R_1	ν_{NH} Stretch Cm^{-1}	ν_{NH_2} Cm^{-1}
p-Br (C_6H_4)	C_6H_5	3290 (S)	——
C_6H_5	CH_3	3350 (M)	——
p-Br (C_6H_4)	CH_3	3318 (S)	——
C_6H_5	C_6H_5	3280 (S)	——
	C_6H_5	3340-3100 (S) Broad	——

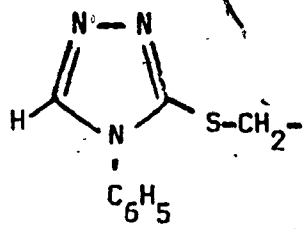
TABLE XI SIGNIFICANT IR FREQUENCIES IN THE SPECTRA OF 2,4 DISUBSTITUTED THIOSEMICARBAZIDES



R	R_1	ν_{NH} Cm^{-1}	ν_{NH_2} Cm^{-1}
CH_3	C_6H_5	3250 (S) 3280 (S)	1625 Cm^{-1} (M)
$P\text{-}OCH_3(C_6H_4)$	C_6H_5	3240 (SH) 3260 (S)	1615 Cm^{-1} (M)
CH_3	CH_3	3265 (S) 3320 (S)	1630 Cm^{-1} (S)
$P\text{-}OCH_2(C_6H_4)$	CH_3	3350 (S) 3340 (SH)	1610 Cm^{-1} (M)

TABLE XII SOME IR FREQUENCIES IN THE SPECTRA OF THE HETEROCYCLIC DERIVATIVES.

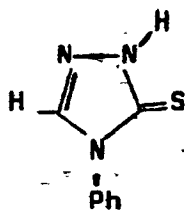


R_1	R_2	Absorption in The $\bar{\nu}$ NH Region Cm^{-1}	$\bar{\nu}$ S – H Cm^{-1}	Absorption in the $\bar{\nu}$ N – C = S Region Cm^{-1}
H	Ph	3100–3300 (S)	——	1290 (W) 1225 (S)
Ph	Ph	3100–3220 (S)	——	1335 (M) 1275 (M)
Ph	H	3100–3270 (S)	——	1325 (M) 1300 (M)
Ph		3110–3200 (M)	——	1325 (S) 1285 (M)

NUCLEAR MAGNETIC RESONANCE SPECTRA

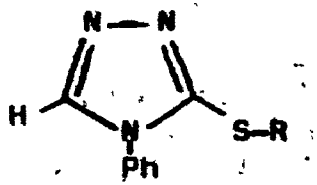
The experimental conditions have been described previously. The nuclear magnetic resonance assignment data for the series of 4-phenyl-5-substituted 1,2,4-triazoles prepared, is summarized in tables XIII through XIV. Coupling constants have been reported where possible. The data substantiate the structure assignments made for these hetrocyclic compounds.

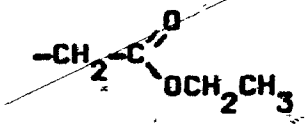
TABLE XIII NMR SPECTRA PARAMETERS OF 4-PHENYL-1,2,4-TRIAZOLINE-5-THIONE

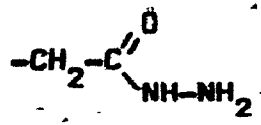


N - 1 Proton	C - 3 Proton	N - Ph Protons
13.8, 1 H (S)	8.67, 1 H (S)	7.58 (7.23-7.83), 5H

TABLE XIV NMR SPECTRAL PARAMETERS OF THE 5-MERCAPTO SUBSTITUTED-4-PHENYL-1,2,4-TRIAZOLE COMPOUN



R	C-3 Proton	N-PH Protons	S-CH_2 Protons	O-CH_2 Protons	C
	8.88, 1H(S)	7.58 (7.32-7.77),5H	4.09, 2H(S)	4.19, 2H (Quartet). J = 7 H_2	1. (J

R	C-3 Proton	N-PH Protons	S-CH_2 Protons	N-H Proton	N
	8.83, 1H(S)	7.55 (7.35-7.67),5H	3.88, 2H(S)	9.30, 1H(S)	4

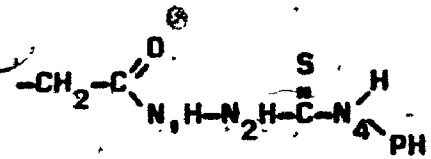
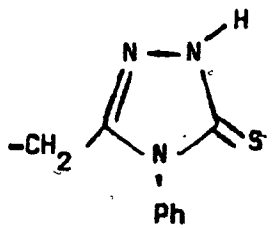
R	C-3 Proton	N-PH Protons	S-CH_2 Protons	N_1-H Protons	N_2-H Protons
	8.87, 1H(S)	Overlapped With N_4-PH 7.57 (7.08-7.70),10H	3.98,2H(S)	Overlapped With N_2-H	9.67,2H(S)

TABLE XIV Cont'd

R	C-3 Proton	N-PH Protons	S-CH_2 Protons	N'-1 Proton	N'-PH Protons
	8.83,1H(S)	Overlapped with N'-PH	4.10,2H(S)	13.8,1H(S)	7.50 (7.13-7.70) 10 H

SUMMARY

The reaction of mono-substituted hydrazines with alkyl or aryl isothiocyanates can be synthetically useful if the reaction conditions and substituents on the hydrazine molecule are chosen so that either the 1,4- or 2,4-disubstituted thiosemicarbazide is formed exclusively. It has been found that low reaction temperatures and electron donating substituents on the hydrazine molecule favour the 2,4-isomer whereas high reaction temperatures and electron withdrawing substituents favour the 1,4-isomer. The yields are quite variable, ranging generally from 30 - 80%. The constitution of an isomer can be determined from infrared spectroscopy since only the 2,4-disubstituted thiosemicarbazide has an NH_2 deformation band in the region of 1600 - 1650 Cm^{-1}.

Investigation into the isomerization of several 2,4-disubstituted thiosemicarbazides suggest that an intramolecular pathway, possibly through a diaziridine type intermediate, is involved.

Mono and disubstituted 1,2,4-triazoline-5-thiones are prepared in good yields (~70%) by either reacting thiosemicarbazides with ethyl formate or by cyclizing 1-benzoylthiosemicarbazides in base. Acid cyclization of 1-benzoylthiosemicarbazides lead

to the formation of isomeric 1,3,4-thiadiazoles. Only the 1,3,4-thiadiazoles absorb in the 300 NM region of the ultra violet spectrum and this difference can serve as a basis for distinguishing these compounds.

A reaction sequence, starting with 1,2,4-triazoline-5-thiones and leading to the preparation of novel 1,2,4-triazole-1,2,4-triazoline-5-thione compounds linked by a methyl mercapto group has been identified. It consists of four separate reactions with an overall yield of about 30%. The following 1,2,4-triazole derivatives obtained in this investigation were new compounds:

3-phenyl (1,2,4-triazolyl-5) mercapto acetate.

1-[4'-phenyl-5'(1,2,4-triazolyl)] mercapto acetyl-4-thiosemicarbazide.

4-phenyl-5 [4'-phenyl-3'-(1,2,4-triazoline-5-thione)] methyl mercapto 1,2,4-triazole.

4-phenyl-5- [5'-phenyl amino) -2' (1,3,4-thiadiazole)] methyl mercapto 1,2,4-triazole.

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